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Survival Modelling for Patients with End Stage Renal Failure: Implications for Access to Renal Transplantation in the UK

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DECLARATION

I declare that this thesis is an original report of my research and has been composed solely by myself. The work was conducted as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme. The studies contained within this thesis were designed by myself and my supervisors with advice from the other ATTOM investigators. Baseline data were collected by research nurses and outcome data were retrieved from the UK Transplant Registry and the UK Renal Registry databases. Data analysis was conducted by myself with input from the statistics department at NHS Blood and Transplant. I confirm that the work presented herein has not been submitted for any other degree or professional qualification.

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advice with the statistical analyses and for providing me with the registry outcome data.

It goes without saying that this project would not have been possible without the cooperation, patience and generosity of the staff and patients in all of the transplant centres across the UK. The participation of all UK centres in a prospective cohort study of this scale is unprecedented. The combined effort of the whole transplant community and their dedication to research and improving outcomes is astounding. I would also like to thank the research nurses who worked tirelessly across the country in order to collect the data within the study deadlines.

Finally, I want to thank Pete, my family and my friends for their love and support. I would not have been able to complete this work without them.

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ABSTRACT

Kidney transplantation has revolutionised the treatment of end stage renal disease (ESRD), offering a significant increase in life expectancy, quality of life and cost-effectiveness when compared with dialysis. However, the provision of transplantation is under immense pressure due to the vastly insufficient number of donor organs, the growing incidence of ESRD and the increasing age and burden of comorbidity of the ESRD population. There is evidence for considerable disparities in access to transplantation across transplant centres in the UK and in the outcomes and prognosis of individual patients. This raises complex issues regarding the assessment of patient suitability for transplantation, maximisation of transplant outcomes and equitable access to transplantation at an individual as well as a societal level.

The aims of this thesis were to address the following key questions:

1) What factors may be contributing to inequity in access to transplantation in the UK?

2) How do patient factors including comorbidity affect graft and patient survival after renal transplantation, and do survival rates differ between centres in the UK?

3) Do patient reported outcome measures differ after living and deceased donor kidney transplantation?

4) What factors affect the survival of patients on dialysis, and can these risk factors be quantified in a survival prediction score aimed at reducing inequity and standardising access to the waiting list?

The research was conducted as part of the national prospective cohort study Access to Transplantation and Transplant Outcome Measures (ATTOM), which is the first study to include ESRD patients from all 72 renal units in the UK. The study included a total of 6844 patients recruited into three different cohorts; incident dialysis, incident transplant and prevalent matched control waiting list cohorts.

The findings showed significant variation between UK centres with regard to the level of comorbidity among patients accepted to the waiting list and to transplantation. Thus, centre differences in selection criteria, patient assessment and risk tolerance are likely to be contributing to inequity in access to transplantation across the UK.

The data highlighted significant socio-demographic differences between dialysis, waiting list and transplant patients. Older, more socially deprived patients and patients with a lower level of educational attainment were significantly less likely to be listed for transplantation. These same groups of patients in addition to patients from ethnic minorities were additionally disadvantaged with regard to undergoing living donor transplantation and pre-emptive transplantation. Geographic factors also contributed to disparities in living donor transplantation.

The key comorbid conditions that predict poorer two year graft and patient survival after kidney transplantation were identified. Peripheral vascular disease and obesity were associated with a higher risk of graft failure, while cerebrovascular disease, heart failure and chronic liver disease were associated with inferior patient survival after transplantation. The risks associated with these conditions have been quantified and can be used to fully inform patients of their individual risks, thereby facilitating shared decision-making and informed consent. Contrary to previous reports, there was no evidence of any inter-centre variation in survival outcomes of transplant patients in the UK.

Living donor kidney transplantation was associated with better patient reported health status, wellbeing, quality of life and treatment satisfaction compared with deceased donor kidney transplantation. Patients who underwent pre-emptive transplantation reported significantly worse treatment satisfaction compared with patients who received a period of dialysis prior to transplantation.

Analysis of patients on dialysis showed that older age, female gender, lower serum albumin, being underweight or having diabetes, heart failure, atrial fibrillation, chronic respiratory disease, chronic liver disease or malignancy were important predictors of mortality within two years of starting dialysis. These results were developed into a survival prediction score that was internally validated. This score could be easily implemented in the clinical setting to provide patients with individual survival prediction and could also be used as a tool to aid listing decisions.

The findings of this thesis have the ability to positively impact the care of patients with ESRD by driving initiatives to reduce inequity in access to transplantation, targeting disadvantaged patient groups, providing individual survival prediction for patients, informing national guidelines for fairer transplant listing and allocation and guiding future research into improving outcomes for all patients.

LAY SUMMARY

Patients with end stage renal disease (ESRD) require renal replacement therapy in the form of dialysis or kidney transplantation in order to survive. Transplantation is associated with better life expectancy, quality of life and cost-effectiveness when compared with dialysis. However, for some patients, transplantation may not be the best option due to their overall health, meaning that the operation is high risk and may not be beneficial. This is an important issue because the number of people who potentially fall into this category is increasing, and also because there is a shortage of donors. Currently, there is no clear consensus on which patients should be considered suitable for transplantation and there is evidence that practice varies across the transplant centres in the UK.

The aims of this thesis were to address the following key questions:

1) What factors may be contributing to inequity in access to transplantation in the UK?

2) How do patient factors including comorbidity affect graft and patient survival after renal transplantation, and do survival rates differ between centres in the UK?

3) Do patient reported outcome measures differ after living and deceased donor kidney transplantation?

4) What factors affect the survival of patients on dialysis, and can these risk factors be quantified in a survival prediction score aimed at reducing inequity and standardising access to the waiting list?

The research was conducted as part of the national prospective cohort study Access to Transplantation and Transplant Outcome Measures (ATTOM), which is the first study to include ESRD patients from all 72 renal units in the UK. The study included a total of 6844 patients recruited into three different groups; incident dialysis (new patients starting dialysis), incident transplant (new patients receiving a transplant) and prevalent matched control waiting list (existing patients already on the waiting list, matched to the transplant group so that they have similar patient characteristics).

The findings showed that some centres in the UK were accepting higher risk patients for transplantation compared with other centres. Thus, there is no clear consensus across the UK as to which patients should be considered suitable for transplantation and this may result in a post-code lottery i.e. patients seen in one hospital may be less likely to be accepted for transplantation than if they were seen in another hospital elsewhere.

Patients who were older, from poorer backgrounds and with a lower level of education were less likely to be on the waiting list for transplantation. These groups of patients in addition to patients from ethnic minorities were also less likely to undergo living donor transplantation and pre-emptive transplantation (transplantation without prior dialysis). Geographic factors also contributed to disparities in living donor transplantation.

The health conditions that predict poorer two year graft and patient survival after kidney transplantation were identified. Peripheral vascular disease and obesity were associated with a higher risk of the kidney transplant failing, while cerebrovascular disease, heart failure and chronic liver disease were associated with a higher risk of death after transplantation. The risks associated with these conditions have been quantified and can be used to ensure that patients are fully aware of their individual risks before agreeing to go ahead with a transplant. Contrary to previous reports, there was no evidence of any difference in survival outcomes of transplant patients treated in different transplant centres across the UK.

Living donor kidney transplantation was associated with better patient reported health status, wellbeing, quality of life and treatment satisfaction compared with deceased donor kidney transplantation. Patients who underwent pre-emptive transplantation reported significantly worse treatment satisfaction compared with patients who received a period of dialysis prior to transplantation.

Analysis of patients on dialysis showed that older age, female gender, lower serum albumin, being underweight or having diabetes, heart failure, atrial fibrillation, chronic respiratory disease, chronic liver disease or malignancy had a higher risk of death within two years of starting dialysis. These results were developed into a score that could be used to help predict the likelihood of survival of patients on dialysis, and it could also be used as a tool to aid

decisions about which patients should be accepted onto the transplant waiting list.

The findings of this thesis have the ability to positively impact the care of patients with ESRD by driving initiatives to reduce inequity in access to transplantation, targeting disadvantaged patient groups, providing individual survival prediction for patients, informing national guidelines for fairer transplant listing and allocation and guiding future research into improving outcomes for all patients.

ABBREVIATIONS

APD	Automated peritoneal dialysis
ABPI	Ankle brachial pressure index
ATTOM	Access to Transplantation and Transplant Outcome Measures
BMI	Body mass index
CABG	Coronary artery bypass graft
CAPD	Continuous ambulatory peritoneal dialysis
CCI	Charlson comorbidity index
CI	Confidence interval
CIT	Cold ischaemic time
CKD	Chronic kidney disease
cRF	Calculated reaction frequency
CVA	Cerebrovascular accident
DBD	Donor after brain death
DCD	Donor after circulatory death
DDKT	Deceased donor kidney transplantation
DGF	Delayed graft function
EQ-5D	EuroQoL five dimensions
ESRD	End stage renal disease
HD	Haemodialysis
HDF	Haemodiafiltration
HLA	Human leukocyte antigen
IQR	Interquartile range

IRODaT	International Registry on Organ Donation and Transplantation
KHA-CARI	Kidney Health Australia - Caring for Australasians with Renal Impairment
KO	Kidney only
LDKT	Living donor kidney transplantation
MM	Mismatches
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIHR	National Institute for Health Research
NSTEMI	Non-ST segment elevation myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
PD	Peritoneal dialysis
pmp	Per million population
PROMs	Patient reported outcome measures
PVD	Peripheral vascular disease
RDQoL	Renal-Dependent Quality of Life
RRT	Renal replacement therapy
RTSQc	Renal Treatment Satisfaction Questionnaire change version
RTSQs	Renal Treatment Satisfaction Questionnaire status version
SE	Standard error
SPK	Simultaneous pancreas-kidney
SRR	Scottish Renal Registry
STEMI	ST segment elevation myocardial infarction
TIA	Transient ischaemic attack

UK	United Kingdom
UKRR	UK Renal Registry
US	United States
W-BQ12	12-item Well-being Questionnaire
WHO	World Health Organisation

CHAPTER 1

Introduction

1.1. Treatment options for end stage renal disease

End stage renal disease (ESRD) is an irreversible loss of renal function defined as a glomerular filtration rate of <15 ml/min/1.73 m^2.[1] It represents the final stage of chronic kidney disease (CKD) and patients require renal replacement therapy (RRT) in the form of dialysis or renal transplantation in order to survive. Although CKD is asymptomatic, the decline in renal function that leads to ESRD eventually results in manifestations such as fluid overload, anaemia, hypertension, hyperkalaemia and symptoms related to uraemia which may include nausea, anorexia, fatigue, malnutrition, bone disease and neuropathy. In the UK the leading cause of ESRD is diabetic nephropathy, and other common causes include glomerulonephritis, polycystic kidney disease, renal vascular disease, hypertension and pyelonephritis.[2] This embodies a diverse spectrum of patients across all ages, with varying levels of comorbidity. Deciding on the optimal RRT modality for individual patients is challenging and may be subject to uncertainty and subjectivity from patients and professionals alike, and evidence shows there are significant variations in practice throughout the UK.[3-6]

1.1.1. Transplantation

In just 50 years, kidney transplantation has undergone a dramatic transformation, from an experimental procedure to a highly successful and established treatment that has revolutionised the management and prognosis of ESRD. Innovations in surgical technique, immunosuppression, organ preservation and stem cell technology have propelled transplantation to the forefront of pioneering medicine. In selected patients, kidney transplantation

offers up to a three-fold increase in life expectancy, improved quality of life and better cost-effectiveness, compared with dialysis.[7-10] The potentially negative aspects of transplantation include the risks of the major operation and lifelong immunosuppression which comes with increased risk of malignancy, infections, cardiovascular disease and psychiatric disease.

Kidneys may be donated from living donors, donors after brain death (DBD) or donors after circulatory death (DCD). The critical shortage of donor organs is arguably the greatest limitation and challenge currently facing the field of transplantation worldwide. The shortage of organ donors has led to the emergence of unethical practices in transplantation. In less economically developed countries, organ trafficking, transplant commercialism and transplant tourism have become a major issue, resulting in the exploitation of vulnerable and deprived populations through the removal and sale of organs. These practices are prohibited by The World Health Organisation (WHO) Guiding Principles on Human Cell, Tissue and Organ Transplantation[11] and The Declaration of Istanbul,[12] which provide international ethical standards for organ transplantation.

In the UK, significant progress has been made in the past decade to reduce the discrepancy between the number of patients on the waiting list and the number of available donors. Training, clinical and organisational improvements have led to a progressive increase in the number of deceased kidney donors and transplants and a decrease in the size of the waiting list over for the last 9 consecutive years (Figure 1.1).[13]

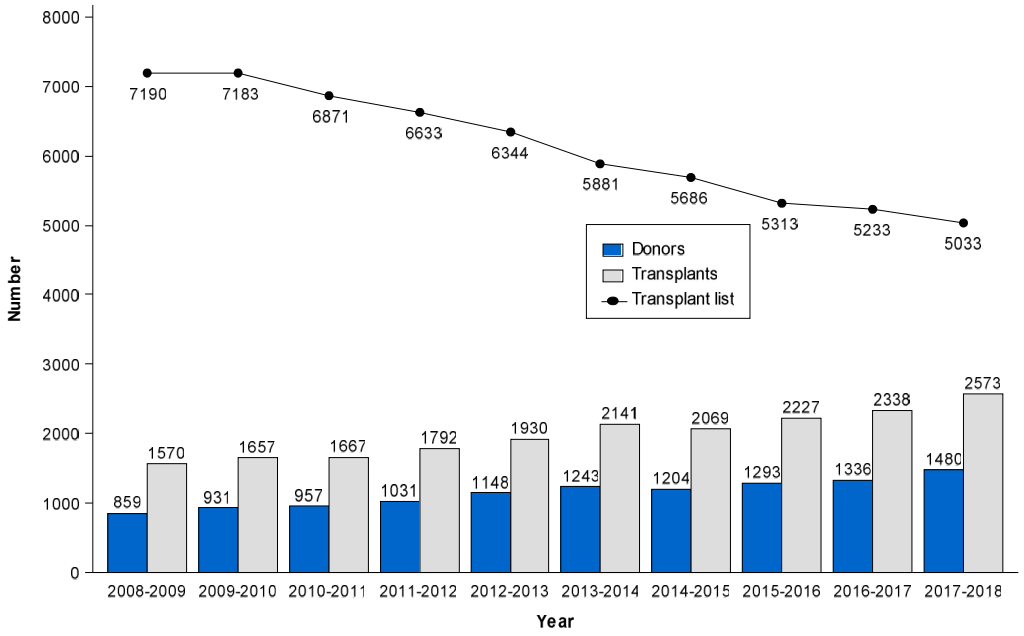

Figure 1.1. UK deceased donor kidney programme. Number of donors, transplants and patients on the active kidney transplant list at 31 March 2018. (Source: NHS Blood and Transplant Organ Donation and Transplantation Activity Report 2017/2018)[13]

Although this is a remarkable achievement, there is still more progress to be made. The decrease in the number of active patients on the waiting list has corresponded with a steady increase in the number of patients suspended from the waiting list (Figure 1.2). The primary reason for suspending patients from the waiting list is a deterioration in the patient's health which means they are no longer fit enough to undergo transplantation. Suspension can be temporary or permanent. In 2017-2018, 3203 patients were suspended from the list, a further 439 patients were permanently removed from the list and 245 patients died whilst on the list. This is concerning and may represent the increasing age and comorbidity of the ESRD population. The current median waiting time for deceased donor kidney transplantation (DDKT) is 2.1 years. An increasing proportion of patients on the waiting list do not have sufficient health to survive this wait. Identifying these patients through accurate

survival prediction at the start of dialysis would improve prognostication and management of the waiting list.

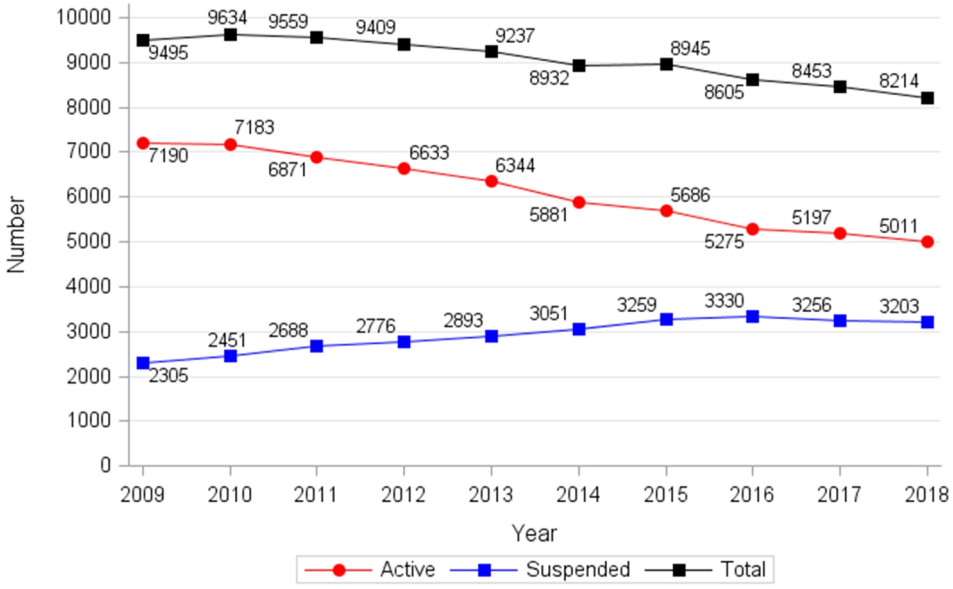

Figure 1.2. Number of patients on the kidney transplant waiting list 2009–2018. (Source: NHS Blood and Transplant Annual Report on Kidney Transplantation 2017/2018) [14]

In the UK, living donor kidney transplantation (LDKT) accounts for around 30% of all kidney transplants[14] and this is fairly representative of most western countries.[15] In contrast, in many Asian and Middle Eastern countries such as Japan, South Korea and Turkey the vast majority of transplants are from living donors, due to the lack of cultural acceptance of deceased organ donation.[16, 17] LDKT is associated with significantly better graft and recipient survival compared with DDKT.[18] The UK Transplant Registry at NHS Blood and Transplant (NHSBT), holds information relating to donors, recipients and outcomes for all kidney transplants performed in the UK. The latest figures from NHSBT show a survival difference of up to 19% at 10 years for LDKT

versus DDKT (10 year patient survival: LDKT 91%, DBD 76%, DCD 72%; 10 year graft survival: LDKT 82%, DBD 76%, DCD 76%).[13] Living donor organs have not been exposed to the detrimental effects of the dying process or prolonged periods of ischaemia, thus leading to optimal post-transplant organ function. LDKT also provides other advantages over DDKT: the transplant procedure can be scheduled electively at a time when both donor and recipient health are optimal, patients avoid long waiting times and the exposure to pre-transplant dialysis and its morbidity is minimised or avoided. For these reasons, LDKT provides the greatest chance of undergoing pre-emptive transplantation, which is associated with significantly better outcomes than transplantation after the initiation of dialysis.[19, 20] Pre-emptive rates are 40% and 16% in LDKT and DDKT respectively.[13] Living donors are usually relatives, spouses or friends of the patient. However, altruistic donation, where the donor does not have a genetic or pre-existing emotional relationship with the recipient, accounts for an increasing number of transplants (Figure 1.3).[14] Sharing schemes have also been developed to enable blood or human leukocyte antigen (HLA) incompatible donor-recipient pairs to be matched with other incompatible pairs, in order to achieve compatible transplants. The clear benefits of LDKT have led to a drive to increase living donation rates, and this has been identified as a major priority for transplantation in the UK.[21] Despite this, the advantages of LDKT must be carefully weighed against the small but not insignificant risks to the donor,[22-25] and their safety and welfare should always take precedence over the need for transplantation.[26]

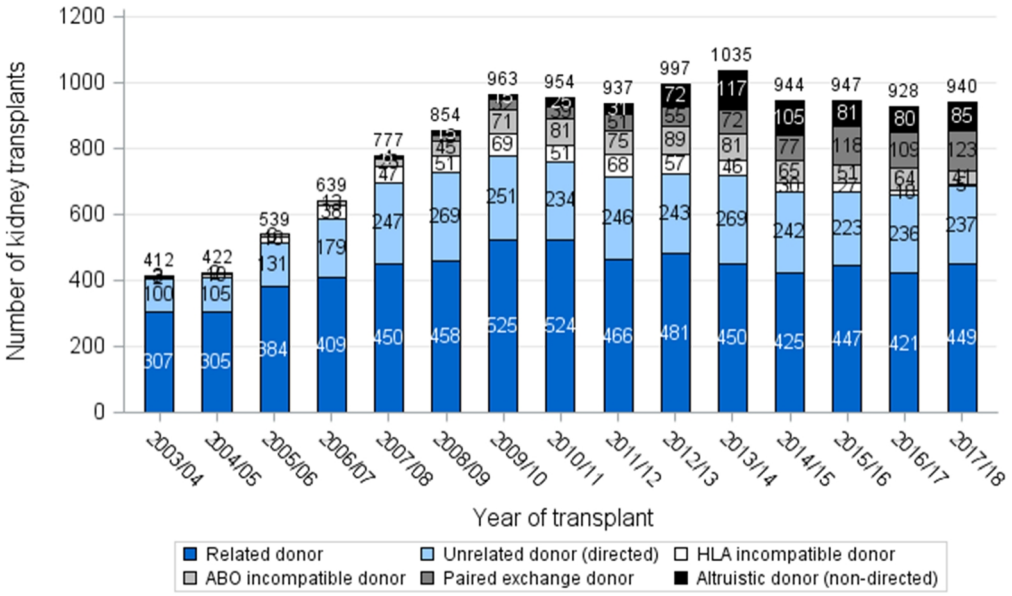

Figure 1.3. Adult living donor kidney transplants in the UK 1 April 2003 – 31 March 2018 (Source: NHS Blood and Transplant Annual report on Living Donor Kidney Transplantation 2017/2018)[27]

Worldwide, the majority of kidneys transplanted from deceased donors are recovered from DBD donors. The concept of brain death was first proposed by Harvard Medical School in 1967.[28] Advances in intensive care techniques meant that comatose patients could be maintained on mechanical ventilation, despite loss of brainstem function and associated loss of the capacity for spontaneous respiration and consciousness. Therefore, it was proposed that such cases of irreversible coma due to permanent damage to the brain could be defined as death.[28] Subsequently, the concept of brain death was gradually accepted elsewhere. The diagnosis of brain death is confirmed by strict neurological criteria which differ considerably between countries. Conversely, in DCD, donation occurs after the irreversible cessation of cardiorespiratory function. The clinical scenario in which cardiorespiratory arrest occurs can be classified into four different categories known as the Maastricht

Classification, which were first described in 1995[29] and subsequently updated in 2013.[30] DCD donations are most commonly Maastricht category III or so called "controlled" DCD. This is usually in the context of a critically ill patient with catastrophic brain injury who does not fulfil the criteria for brainstem death, but where life-sustaining cardiorespiratory support is no longer considered to be in the patient's best interests and is withdrawn under controlled circumstances. Transplantation of DCD donors is still an emerging concept and not universally accepted.[31] However, in some countries including the UK and the Netherlands, DCD donation now accounts for around half of all deceased donations.[14, 31] This is due to the need to expand the donor pool and the growing evidence that the long-term outcomes of DCD and DBD kidney grafts are comparable.[32, 33] In order to receive a kidney graft from a deceased donor, patients must be allocated a kidney according the national kidney allocation scheme (see section 1.2.2).

1.1.2. Dialysis

Although transplantation has superior outcomes compared with dialysis, for some patients, transplantation may not be suitable. Due to comorbidity or frailty, the risk of the transplant procedure may outweigh the potential benefits. Other patients may lack an available donor or may decide against transplantation through their own choice. Dialysis may be administered in the form of haemodialysis or peritoneal dialysis. There are no randomised controlled trials comparing the two dialysis modalities but observational research suggests equivalent survival outcomes.[34-36] Dialysis is an intensive therapy. Haemodialysis usually requires at least three sessions of around four hours every week while peritoneal dialysis usually involves around four

exchanges every day (although this can be done at night using an automated machine).[37] Both modalities can be administered either at a dialysis facility or at the patients home. Home based therapy is associated with significantly better quality of life and promotes independence and self-efficacy in patients in managing their disease.[38, 39] During dialysis, solutes are removed from the body by diffusion across a semipermeable membrane (or in peritoneal dialysis, across the peritoneal membrane) and ultrafiltration is used to remove fluid. However, dialysis can only provide around 10% of the solute clearance of normal renal function.[37] Therefore patients on dialysis often continue to suffer from uraemic symptoms and are at significant risk of progressive cardiovascular disease. In some elderly patients with extensive comorbidities, dialysis may not improve their length or quality of life, and the patient may opt for conservative treatment of their symptoms rather than undergoing dialysis.

1.2. Access to renal transplantation

In order to receive a kidney transplant, patients must undergo a two-step process. First, they must be accepted on the waiting list, and second, they must either be allocated a deceased donor kidney via the national allocation algorithm or else they must find a suitable living donor.

1.2.1. Access to the transplant waiting list

For most patients with ESRD, kidney transplantation offers the greatest potential for achieving a healthy life. However, not all patients are suitable candidates for transplantation. There are relatively few contraindications to transplantation in the UK (Table 1.1.), and access to the waiting list is often determined by an assessment of the perceived risks and benefit for individual patients. Estimation of risk is a key part of the evaluation process for transplantation. This is particularly pertinent when considering the fact that the ESRD population often have a complex medical history and high prevalence of comorbidity.

Table 1.1. Contraindications to transplantation in the UK

Absolute contraindications
Uncontrolled cancer
Active systemic infections
Any condition with a life expectancy < 2 years
Relative contraindications
Predicted patient survival < 5 years
Predicted risk of graft loss > 50% at 1 year
Patients unable or unlikely to adhere with immunosuppressant therapy
Immunosuppression predicted to cause life threatening complications

Source: Adapted from NHSBT Patient Selection for Deceased Donor Kidney Only Transplantation Policy[40]

Various patient and centre factors have been shown to influence access to the transplant waiting list. A study by Oniscu et al. in 2003 demonstrated major disparities for patients in Scotland in the likelihood of being placed on the renal transplant waiting list and of receiving a kidney transplant.[4] Two subsequent UK studies confirmed these findings, and found that inequities also existed for patients in England and Wales.[3,5] The findings of these studies are summarised in Table 1.2.

Table 1.2. Patient- and centre-specific factors influencing access to the deceased donor kidney transplant waiting list

Reference	Study Design	Factors negatively impacting access to the waiting list
Oniscu et al. 2003	Longitudinal cohort	Older age, female, diabetes, high deprivation category, treated in non-transplanting renal unit, centre effect
Dudley et al. 2009	Cross-sectional	Older age, diabetes, high deprivation category, comorbidity, treated in smaller renal unit, centre effect
Ravanan et al. 2010	Longitudinal cohort	Older age, diabetes, non-white ethnicity, treated in non-transplanting renal unit, centre effect

It is well-recognised that various patient factors including age, gender, social deprivation and ethnicity act as barriers to wait-listing, and this has also been shown to be the case in countries outside of the UK.[41-45] The reasons for these disparities are not fully understood, and are likely to represent a complex interaction between comorbidity, clinical, socioeconomic, lifestyle and cultural factors.[46] Due to the poor understanding of these disparities, there have been a lack of effective solutions, leading to the persistence of inequity in access to transplantation. Furthermore, although it is known that these factors affect access to DDKT, at the time of conception of the ATTOM study,

little work had been done to investigate whether similar barriers existed in access to LDKT. More recently, research to address this gap in knowledge is now emerging, including qualitative studies exploring disparities in LDKT in the UK.[47, 48]

A finding of additional concern is that the renal centre in which a patient is treated significantly affects the likelihood of listing for transplantation. For example, in the study by Oniscu et al., patients starting dialysis in a transplanting unit had a 28% better chance of listing compared with those treated in non-transplanting units.[4] This evidence for an apparent "post-code lottery" may imply differences in centre protocols, organisational aspects or disparities in clinicians' estimation of patient risk in the context of kidney transplantation. Akolekar et al. showed that the assessment processes for determining patient suitability for renal transplantation and the acceptance criteria used, varied widely across the UK.[6] Some centres lacked a formal assessment clinic and/or multidisciplinary team meeting suggesting that patient cases may not be discussed with other members of the transplant team prior to making a decision about listing, and that patients may not be seen by a surgeon until being admitted for the actual transplant procedure.[6] A similar UK study also demonstrated inconsistencies in the attitudes towards patient selection for renal transplantation, amongst nephrologists and transplant surgeons across the country.[49]

All of these issues are not surprising given the lack of clear and consistent guidance on access to transplantation.[50] Given the increasing prevalence of higher risk patients with significant comorbidity in the ESRD population,

more and more decisions will need to be made regarding the optimal treatment for these patients, in whom the survival advantage of transplantation may be less certain. Currently, there is a lack of an agreed and clear definition for "high risk" patients and the available evidence on the outcome for such patients is limited and conflicting.[51-55] As the NHS strives towards reducing variations in the quality of administered medical care irrespective of where a patient is treated, the inequity of care that is evident across the UK for ESRD patients is clearly an issue that needs to be prioritised and addressed. There is a need to establish clear, national, evidence-based guidelines, in order to reduce inequities in care and maximise outcomes for all patients with ESRD. The development of a survival probability score could guide clinicians in the estimation of risk in the context of kidney transplantation, leading to more objective and standardised access to the waiting list.

1.2.2. Allocation of donor kidneys

The ongoing shortage of donor kidneys means that allocation of this scarce resource is increasingly challenging and complex. In the US, the number of patients on the waiting list has doubled over the past decade reaching around 100 000 patients, median waiting time has increased by 50% to over 4.5 years and nearly 5000 patients die whilst waiting for a deceased donor kidney transplant every year.[56] In the UK, significant progress has been made in recent years in promoting organ donation and transplantation,[57] resulting in a fall in the number of patients on the waiting list. However, in 2018 there were still 5033 patients waiting for a transplant with a median waiting time of 2 years.[13] Moreover, between 2017-2018 in the UK, 245 patients died whilst

waiting for a kidney transplant and 439 patients were removed from the list (typically due to clinical deterioration resulting in becoming unsuitable for transplantation).[13]

The allocation of deceased donor kidneys raises an ethical dilemma centred on the competing values of utility (maximum outcomes) and equity (fairness). Consideration must be given to the efficient use of organs to optimise outcomes and the overall benefit to society, but also to the welfare of individual patients and fair access to transplantation.[58] Utility-based allocation prioritises patients with the best chance of a favourable outcome, aiming to achieve the maximum benefit from every transplanted organ. Inevitably, this gives rise to debate over how benefit should be measured – i.e. graft survival, patient survival, life years gained from transplant or quality of life? Furthermore, it disadvantages patients less likely to experience a good outcome, such as patients who are older, diabetic, have more comorbidity or have been on dialysis for a longer period of time.[19, 59-62] An increasing proportion of patients on the waiting list fall into these categories, yet still derive a significant survival benefit from transplantation.[7, 63-65] The principle of equity necessitates fairness in organ allocation, however this may be interpreted in various ways. Equity is commonly conceived as "equal opportunity" i.e. every person who may benefit from a transplant should have equal opportunity of receiving one.[66] It is important not to misinterpret this as equality; although equality involves treating all patients exactly the same (i.e. allocation by lottery), it neglects the fact that patients do not start from equal circumstances.[67] The discovery of HLA-matching as a major determinant of graft survival led to its principal role in the first formal allocation

schemes.[68-70] However, it became apparent that such schemes resulted in inequitable access to transplantation for difficult to match patients.[71-73] Consequently, most schemes now award extra priority to highly-sensitised patients and patients with rare HLA-types (most commonly from ethnic minorities) who are biologically disadvantaged in finding a compatible donor, in order to equalise their opportunity for transplantation. “Queuing” (first-come, first-served) is another concept of equity that has been widely considered in kidney allocation. However, with the increasing age and morbidity of patients on the waiting list, this approach has been challenged for favouring those who are able to survive the ever-increasing wait. Furthermore, with growing evidence for disparities in access to the waiting list, many schemes now measure waiting time from the start date of dialysis as opposed to the listing date, although some countries are yet to adopt this approach. Priority for paediatric patients is universally acknowledged in view of the detrimental impact of renal failure and prolonged dialysis on growth and development (although the age cut-off and level of priority varies substantially between different schemes). In contrast, the prioritisation of younger adults over older adults is widely disputed. While advocates of the “fair innings” concept believe equity should be measured by the opportunity to reach a normal life expectancy, critics argue that preferential allocation to younger patients is age discrimination.[74] The “prudential lifespan” provides an alternative concept of equity through the allocation of kidneys by age-matching. This justifies the allocation of younger (and therefore “higher quality” kidneys) to younger recipients and the allocation of older kidneys to older recipients since all patients are treated similarly in a particular stage of life.[75] However, this approach becomes problematic if there is a discrepancy

in the age distribution of donor and recipient pools. Moreover, age is just one of many factors which influence the outcome of transplanted kidneys.

The current UK national kidney allocation scheme was last modified in 2006. Under this scheme, DBD kidneys are matched to potential recipients according to HLA-type and blood group, and priority is then awarded to recipients based on a patients HLA sensitisation level, HLA homozygosity, paediatric status and the level of the HLA match, in addition to a points score derived from various factors (waiting time, recipient age and HLA match combined, proximity of the donor to the recipient centre, donor-recipient age difference, HLA-DR and HLA-B homozygosity, blood group match), with waiting time being the most influential.[76] The algorithm was developed in response to evidence that the previous utility based scheme of 1998 (which assigned priority to better matched grafts), disadvantaged certain groups of patients (i.e. those with rare HLA types or those highly sensitised).[77, 78] By placing more emphasis on waiting time, the aim was to shift the balance back towards equity. As of September 2014, DCD kidneys were also allocated using the principles of the national allocation scheme, but on a regional basis only and one kidney is always offered preferentially to the local transplant centre (both kidneys are retained locally if the donor is <5 or >64 years).[79]

The current scheme does not give any consideration to the "quality" of the donor kidney, and apart from avoiding extreme age mismatches, there is no attempt to match estimated graft life with estimated patient survival. As a result, donor kidneys with longer estimated survival may be transplanted into recipients with much shorter estimated survival, thus leading to death with a

functioning graft. This translates into the loss of potential benefit from the graft. Higher rates of death with a functioning graft occur with increasing age and comorbidity of recipients,[80-85] and with these patients accounting for a growing proportion of transplant candidates, it is likely that a greater number of functioning grafts will be lost this way. Moreover, in the reverse circumstance, younger patients may be allocated grafts with much shorter estimated survival, which may result in higher rates of re-transplantation and higher levels of sensitisation as well as further increasing the demand for donor organs.

With the ongoing organ shortage crisis that exists worldwide, there is now great interest within the international transplant community in developing organ allocation systems based on net transplant benefit. In the US, a new kidney allocation system based on "longevity matching" has recently been described, whereby a range of survival predictors are utilised to allocate kidneys based on matching of estimated graft and recipient survival.[86, 87] Sophisticated donor-recipient survival matching may well be the optimal compromise between utility and equity that the transplant community strives for.

1.3. Outcomes of patients with end stage renal disease

1.3.1. Survival

The survival benefits of transplantation over dialysis are well recognised. A pivotal study by Wolfe et al. compared a large cohort of transplant recipients and age-matched controls on the waiting list in the US between 1991 and 1997. Despite an initial higher short term risk of mortality, transplantation resulted in an average increase in life expectancy of 10 years.[7] Using similarly constructed studies, comparable results have been reported in Canada, Germany, Sweden and Scotland, despite the lower dialysis mortality in these countries compared with the US.[8, 65, 88, 89] Oniscu et al. investigated the survival benefit of transplantation for patients in Scotland, and demonstrated an overall 12 year increase in projected life expectancy for wait-listed patients who were transplanted, compared with those who remained on dialysis (Figure 1.4.).[8]

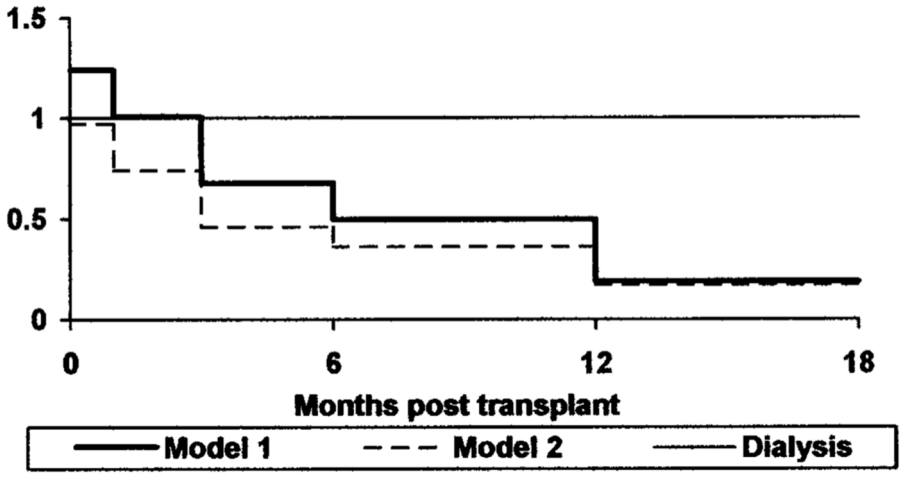

Figure 1.4. Relative risk of mortality over time after transplantation versus diaysis patients on the waiting list in the first 24 months post-transplant. Non-proportional Cox models adjusted for age, gender, primary renal disease, social deprivation, time since wait-listing (model 1), and comorbidity (model 2). (Source: Oniscu et al.[8])

However, the demographics of the ESRD population have changed considerably in recent years. The prevalence of comorbidity and complex multimorbidity is increasing and the survival advantage for such patients may not be as clear. A small number of studies have demonstrated that comorbid conditions are important predictors of mortality on dialysis[90-93] and after transplantation.[62, 94] These studies have largely been retrospective registry or single centre analyses. Further work is required to fully investigate the impact of comorbidity on the survival of ESRD patients in a national prospective cohort study. Shared decision making and accurate communication of risks to patients is increasingly important in the informed consent process. There is a need for up to date evidence to guide treatment decisions in the UK. This work is particularly meaningful in the present context of the shortage of donor organs and has implications for listing and allocation policy.

1.3.2. Patient reported outcome measures

Patient reported outcome measures (PROMS) are increasingly recognised as important goals and indicators of quality of care. In addition to health related quality of life measures, many other outcome measures have been developed to encompass the multidimensional aspects of a patient's life such as psychological well-being and treatment satisfaction. Furthermore, condition-specific PROMS are increasingly used to gain insights into the impact of a patient's specific health condition on their quality of life. Better PROMS have been linked to improvements in key laboratory values, mortality, hospitalisation rates and adherence to therapy.[95-97]

Systematic reviews have not found any statistical difference in PROMS between patients undergoing haemodialysis and peritoneal dialysis, although there is a tendency towards better outcomes with peritoneal dialysis.[98-100]

The obvious benefits of receiving a transplant over remaining on dialysis include the freedom from the intensive treatment schedule of dialysis, increased independence, return to work, freedom from dietary and fluid restrictions, psychological well-being and physical capability. Most studies to date confirm that transplantation improves quality of life over dialysis.[63, 101-103]

There is a lack of research into whether the type of kidney transplant received affects PROMS. The choice of LDKT or DDKT can be a difficult decision for patients and their families, and one that may cause considerable consequences on patients' quality of life and emotional well-being. Some studies have reported that recipients of LDKT experience increased feelings of anxiety and guilt towards the donor after transplantation.[104, 105] Further work is needed to assess whether the drive to increase and promote LDKT rates in the UK based on the clinical benefits, is also validated by PROMS.

1.4. Summary

Kidney transplantation has revolutionised the treatment of ESRD, offering a significant increase in life expectancy, quality of life and cost-effectiveness when compared with dialysis. However, the provision of transplantation is under immense pressure due to the vastly insufficient number of donor organs, the growing incidence of ESRD and the increasing age and burden of comorbidity of the ESRD population. There is evidence for considerable disparities in access to transplantation across transplant centres in the UK and in the outcomes and prognosis of individual patients. This raises complex issues regarding the assessment of patient suitability for transplantation, maximisation of transplant outcomes and equitable access to transplantation at an individual as well as a societal level. There is a lack of high quality studies on how patient and centre factors influence access to and outcomes from renal transplantation in the UK.

1.5. Aims

The aims of this thesis were to address the following key questions in the context of a national prospective cohort study involving all renal units in the UK:

1) What factors may be contributing to inequity in access to transplantation in the UK?

2) How do patient factors including comorbidity affect graft and patient survival after renal transplantation, and do survival rates differ between centres in the UK?

3) Do patient reported outcome measures differ after living and deceased donor kidney transplantation?

4) What factors affect the survival of patients on dialysis, and can these risk factors be quantified in a survival prediction score aimed at reducing inequity and standardising access to the waiting list?

CHAPTER 2

Methods

2.1. Study design

The work within this thesis was conducted as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme, funded by the National Institute for Health Research. This national research programme was designed to identify the reasons for variations in access to renal transplantation across the United Kingdom (UK), and to develop methods to improve outcomes for patients with end stage renal disease (ESRD). The research programme was designed as a UK-wide prospective cohort study and encompassed the following workstreams:

1) Access to the transplant waiting list and access to transplantation
2) Factors affecting survival on dialysis and after transplantation
3) Patient reported outcome measures on dialysis and after transplantation
4) Health economic analyses for alternative approaches to organ allocation

Each workstream was investigated by individual researchers with supervision from a workstream lead. Each team devised the methodology and conducted the research for their own workstream. The primary focus of this thesis was workstream 2, but inevitably there was some crossover, and where relevant it was necessary to conduct some analyses pertaining to themes from other workstreams. The overall research programme was overseen by a steering group which included transplant surgeons, nephrologists, health psychologists, health economists, epidemiologists, statisticians, bioethicists and patient representatives. Members of the steering group are listed in Appendix A.1. The steering group met biannually to evaluate progress within

each workstream and provide feedback. Ultimately the aim was to combine the research from all workstreams and provide a comprehensive scientific basis for the development of new listing and allocation policy in the UK, that achieves the best balance between equity of access, prolongation of life, quality of life, acceptability to patients and society and cost effectiveness.

2.2. Study population

Patients aged 18-75 years were recruited to ATTOM from all 72 UK renal units (of which 23 are renal transplant centres). In each unit, recruitment took place over a 12-month continuous period, at any point between 1st November 2011 and 31st March 2013, aiming to capture all patients starting renal replacement therapy (RRT). There was a total of 6844 registrations to ATTOM, and patients were recruited into three different cohorts: incident dialysis cohort (n=2623), incident transplant cohort (n=2262) and prevalent waiting list cohort (n=1959) (Figure 2.1).

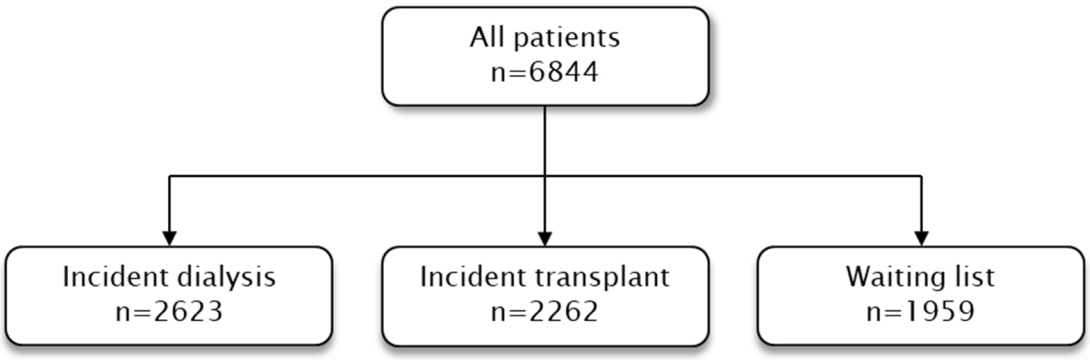

Figure 2.1. ATTOM study population and cohort distribution

Patients were recruited at the time of starting dialysis, at the time of renal transplantation or from the waiting list as matched controls to the transplant patients. All types of renal transplant were eligible for recruitment including living donor, deceased donor, kidney only and simultaneous pancreas-kidney (SPK) transplants. Matched controls were identified from the waiting list on a fortnightly basis and were matched to transplant patients for six criteria (Table 2.1).

Table 2.1. Matching criteria	
1. Transplant centre	Same centre
2. Age	Within −/+ 5 years
3. Time on the waiting list	Within −/+ 100 days if time is ≤1000 days
	Within −/+ 10% if time is >1000 days
	<365 days if unlisted living donor transplant
4. Type of transplant	Kidney only / SPK
5. Diabetic (based on primary renal disease)	Yes / No
6. Pre-emptive	Yes / No

Since the matching process was used to identify waiting list controls, matching occurred prior to their recruitment and therefore prior to the collection of comprehensive data for the study. Thus, matching criteria were based on variables that were available from the UK transplant registry database. Diabetes as a matching criterion was based on primary renal disease rather than any diagnosis of diabetes because the latter is not collected as part of the UK transplant registry database. Although this may have resulted in some loss of accuracy with regards to matching, it is unlikely to have major implications on the analyses. This is because all analyses will be fully adjusted for a comprehensive set of confounding factors including comorbidity, and the extent to which diabetes affects outcomes will be explored using the detail captured in the diabetes variable i.e. any diagnosis of diabetes, diabetes as a primary renal disease, type I diabetes and type 2 diabetes.

The aim of including a matched control cohort was to enable a comparison of outcomes on dialysis to outcomes after transplantation, with minimisation of confounding factors. It would not have been possible to directly compare the incident dialysis cohort to the incident transplant cohort due to the bias

introduced by the selection process for transplantation, which inherently selects a fitter group of patients. Therefore, we aimed to recruit a comparable cohort of ESRD patients who had already been through the selection process for transplantation i.e. patients on the waiting list.

In all, 471 patients changed cohorts within the recruitment period (13 patients changed twice) (Figure 2.2). This occurred when for example, waiting list patients went on to receive a transplant. In this situation, patients were recruited again to the new cohort as a separate registration and therefore contributed data to more than one cohort. There were 6844 registrations to ATTOM and this represented a total of 6360 individual patients.

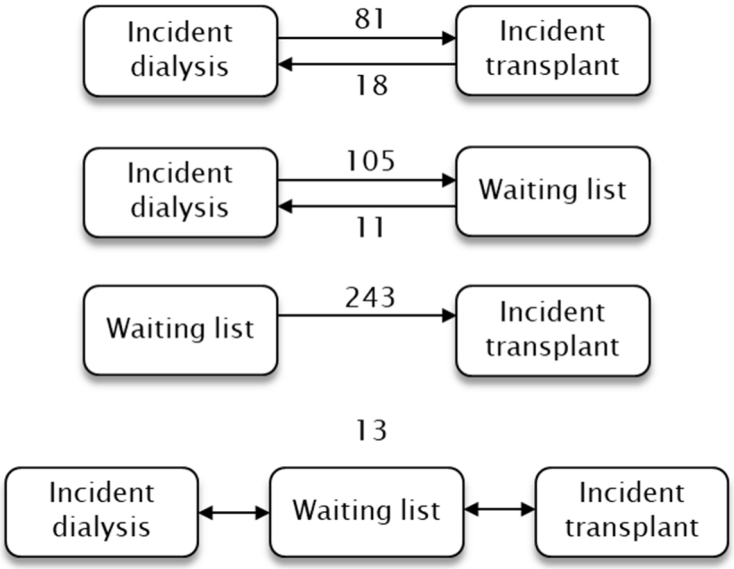

Figure 2.2. Number of patients who changed cohorts

2.3. Data variables

Extensive baseline data were collected prospectively for every patient at the time of recruitment to each cohort. The baseline dataset was designed to capture information on variables that are known or suspected to have an influence on outcomes, including potential confounding factors. Demographic, socioeconomic, clinical and comorbidity variables exceeding that available from national registries were collected for all patients at the time of recruitment. Dialysis, transplant and waiting list specific variables were collected for the respective cohorts (Appendix A.2). Variable definitions are given in Appendix A.3. Data on 16 comorbidity variables were collected for every patient and this data were fundamental to the novelty of the survival analyses within this thesis. From previous retrospective and single centre studies, it is known that comorbidity likely plays a major role in influencing the survival outcomes of patients on dialysis and patients undergoing kidney transplantation. However, comorbidity variables are not routinely collected by national registries, and to date no studies have collected prospective comorbidity data on a national basis, thus ATTOM is the first study to do so. In chapters where the aim was to investigate survival outcomes, the individual comorbidity variables were used in the statistical models. However, in other chapters where the focus was more on how socioeconomic factors influence access to transplantation, the comorbidity variables were combined to create a comorbidity score for each patient using the index described by Hemmelgarn et al.[106] This enabled each patients level of comorbidity to be summarised into a single score, thereby reducing the number of factors (and degrees of freedom) in the predictive models and improving the accuracy of

the effects of the studied socioeconomic variables, while still allowing adjustment for comorbidity. The comorbidity index by Hemmelgarn et al. is based on the widely used Charlson Comorbidity Index (CCI)[107] but is modified to specifically predict the survival of patients with ESRD. The index consists of weighted scores assigned to 14 comorbid conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatological disease, peptic ulcer disease, diabetes without complications, diabetes with complications, leukaemia, lymphoma, moderate-severe liver disease and metastatic disease). Our dataset did not include 2 of the conditions (rheumatological disease and peptic ulcer disease) therefore scores were calculated from the remaining 12 variables (Table 2.2). Definitions for the variables used in the index are given in Appendix A.4.

Table 2.2. Modified Charlson Comorbidity Index

Comorbidity variable	Score
Myocardial infarction	2
Congestive heart failure	2
Peripheral vascular disease	1
Cerebrovascular disease	2
Dementia	1
Chronic pulmonary disease	1
Rheumatological disease	Excluded*
Peptic ulcer disease	Excluded*
Diabetes without complications	2
Diabetes with complications	1
Leukaemia	2
Lymphoma	5
Moderate-severe liver disease	2
Metastatic disease	10

*Not collected in the ATTOM dataset and therefore excluded from the score

The limitations of using the modified CCI were that we were unable to calculate the full score as the ATTOM dataset did not include two of the required variables, and also that the index was originally developed to predict the survival of ESRD patients in Canada, thus its validity in UK ESRD patients is uncertain. However, the aim of using the score was not to predict survival in our cohort, but purely to provide a summary of each patient's level of comorbidity in a single score. Compared to other available comorbidity indices, the modified CCI contained the most similar variables as the ATTOM dataset and has been validated among ESRD patients in multiple countries with good performance.[91, 94, 106, 108-111]

Data on patient reported outcome measures (PROMS) were collected at various time points for patients from all cohorts in the ATTOM research programme. The PROMS data of specific interest to and used for analyses within this thesis included questionnaires measuring patients self-reported health status (EuroQoL five dimensions [EQ-5D-5L] and the EuroQoL visual analogue scale [VAS]), well-being (12-item Well-being Questionnaire [W-BQ12]), general and renal-dependent quality of life (Renal-Dependent Quality of Life Questionnaire [RDQoL]) and treatment satisfaction (Renal Treatment Satisfaction Questionnaire status version [RTSQs] and Renal Treatment Satisfaction Questionnaire change version [RTSQc]). These questionnaires were administered to a subset of patients from the incident transplant cohort at 1 year post-transplantation. Descriptions of the PROMs questionnaires are given in Appendix A.5.

2.4. Data collection

A team of 23 trained research nurses collected the data. Each nurse was based in one of the 23 UK renal transplant centres and also covered that centre's referring renal units (Appendix A.6). The defined baseline dataset was collected from patient interview, case notes, local electronic patient information systems and confirmed with the patients named consultant if required. All data were uploaded in real time onto a secure website using mobile encrypted broadband enabled laptops. PROMs questionnaires were either posted to patients or were completed online and were provided in other languages if required. Research nurses uploaded questionnaire responses to the online database. This was stored on a secure server maintained by the UK Renal Registry (UKRR) which conformed to NHS data protection requirements. An independent validation of 5% of data entries in all research sites confirmed >98% concordance for all data fields. Outcome data including activation on the transplant waiting list and 2 year graft and patient survival are already collected to a high standard by the national registries and as such were obtained through linkage with the UK Transplant Registry, UKRR and Scottish Renal Registry (SRR).

2.5. Statistical analyses

The statistical methods used in each analysis will be provided in detail in each chapter. In general, survival was examined using the Kaplan-Meier method. Appropriate multi-level models (e.g. Cox proportional hazards regression, logistic regression etc.) were developed to analyse the association of patient-level and centre-level factors with the outcomes of interest. All models were built using both statistically significant variables as well as clinically important variables. Potential interactions between variables were tested. Appropriate sensitivity analyses were included. All analyses were conducted using SAS® 9.4 (SAS Institute Inc, Cary, USA).

2.6. Patient and public involvement

Patient representatives were involved in the study from the outset and attended all steering group meetings throughout the duration of the study. Representatives included patients on dialysis, renal transplant recipients and members of the National Kidney Federation (a national kidney charity run by kidney patients). They provided valuable advice on the design of the study, data collection and outcome measures. They ensured that patient views were represented in the conduct and reporting of the study. Lay summaries of the completed research will be jointly produced with the National Kidney Federation who will play a key part in dissemination of the findings to kidney patients across the UK.

2.7. Funding and ethical approval

The ATTOM research programme was funded by the National Institute for Health Research under the grant number RP-PG-0109-10116. The funding body had no role in the study design, data collection, data analysis, data interpretation or writing of this thesis. Ethical approval was granted by the East of England Research Ethics Committee (reference number 11/EE/0120).

CHAPTER 3

Variations in the Comorbidity Burden of Patients Accepted for Kidney Transplantation Across the UK

3.1. Introduction

Kidney transplantation is now widely accepted as the best treatment for end stage renal disease (ESRD). Despite an initial higher risk of mortality in the immediate post-operative period, in the long-term, transplantation offers up to a three-fold increase in life expectancy, improved quality of life and better cost-effectiveness, compared with dialysis.[7-10] With the success and advances of kidney transplantation, many patients who would previously have been deemed unsuitable, are now considered for this treatment option. Nevertheless, such treatment decisions must involve careful consideration of the potential risks that comorbidity may confer on individual patient outcomes. Comorbidity is an important predictor of mortality, but there is a paucity of data on how it affects the risk-benefit ratio of kidney transplantation. This is largely due to difficulties in collecting accurate pre-transplant comorbidity data at a population level. Comorbidities represent a large and heterogeneous group of conditions with differing levels of severity, making precise measurement problematic and time-consuming. The UK Renal Registry (UKRR) attempts to collect national comorbidity data for ESRD patients in the UK but data completeness is poor at around 56% and the Scottish Renal Registry (SRR) does not collect comorbidity data for ESRD patients in Scotland.[112, 113] Other national registries of patients with ESRD in Europe, Japan and the US also lack comprehensive comorbidity information.[114]

With a lack of evidence as to how comorbidity affects post-transplantation outcomes, it is conceivable that variation exists in the interpretation of comorbidity in the context of transplant suitability. Several studies have

demonstrated significant variation in access to kidney transplantation between centres in the UK.[3-5] However, the reasons for these disparities are not well understood and have not been fully explored. Lack of adjustment for comorbidity in these analyses, means that the perceived variation could be explained by some centres having sicker patient populations than others, thereby justifying a lower listing and transplantation rate. On the other hand, centre differences in acceptance criteria for kidney transplantation and in risk tolerance, could be contributing to inequitable access to transplantation.

The aim of this study was to characterise the comorbidity burden of patients starting dialysis, patients on the waiting list and patients receiving a kidney transplant, and determine whether this differs between kidney transplant centres in the UK.

3.2. Methods

3.2.1. Study population

This analysis included all 6844 patients recruited to the ATTOM research programme (2623 dialysis patients, 2262 transplant patients and 1959 waiting list controls). Patients were recruited from all 72 UK renal units (of which 23 are transplant centres) between 1 November 2011 and 31 March 2013. Full recruitment methods are described in Chapter 2.

3.2.2. Data variables

Extensive baseline demographic, socioeconomic, clinical and comorbidity data were collected for each patient, either at the time of starting dialysis, receiving a transplant or identification as a matched control on the waiting list (Appendix A.2). The primary variables of interest in this analysis included comorbidities reported at the time of recruitment to the study, including diabetes, ischaemic heart disease, heart failure, atrial fibrillation, cardiac valve replacement, pacemaker, cerebrovascular disease, peripheral vascular disease, abdominal aortic aneurysm, chronic respiratory disease, chronic liver disease, blood borne viruses, malignancy, mental illness, dementia and obesity (Definitions provided in Appendix A.3). As well as assessing comorbidity by the presence or absence of these conditions, we also calculated a comorbidity score for each patient using the modified Charlson Comorbidity Index (CCI)[106] as described in Chapter 2.

3.2.3. Statistical analysis

Descriptive analyses were used to characterise differences in demographic, socioeconomic, clinical and comorbidity variables between the 3 cohorts and between centres. Baseline characteristics were presented as numbers with percentages (%) compared by chi-squared tests for categorical data and medians with interquartile ranges (IQR) compared with Wilcoxon tests or Kruskal-Wallis tests for non-parametric continuous data. Renal units were grouped to their referral transplant centre for centre analyses (grouping detailed in Appendix A.6). The number of recruited patients in each transplant centre (after grouping of renal units) is shown in Table 3.1. Patients with missing data were excluded from analyses (Table 3.2.). All analyses were carried out using SAS® 9.4 (SAS Institute Inc, Cary, USA).

Table 3.1. Number of recruited patients in each centre				
Centre	Cohort			
	Dialysis n=2623	Waiting List n=1959	Transplant n=2262	Total n=6844
Belfast	95	76	78	249
Birmingham	376	129	121	626
Bristol	135	81	103	319
Cambridge	170	175	196	541
Cardiff	75	69	103	247
Coventry	3	13	25	41
Edinburgh	89	73	99	261
Glasgow	123	97	101	321
Leeds	58	94	107	259
Leicester	72	43	43	158
Liverpool	236	111	111	458
London – Bart's	119	58	69	246
London – Guy's	134	160	202	496
London – Royal Free	67	78	80	225
London – St George's	191	102	93	386
London – West	153	78	92	323
Manchester	84	113	163	360
Newcastle-upon-Tyne	62	78	94	234
Nottingham	63	62	64	189
Oxford	27	109	146	282
Plymouth	31	28	40	99
Portsmouth	106	78	77	261
Sheffield	154	54	55	263

Table 3.2. Missing data			
	Dialysis n=2623	Waiting List n=1959	Transplant n=2262
Demographic variables			
Age	0 [0%]	0 [0%]	0 [0%]
Gender	0 [0%]	0 [0%]	0 [0%]
Ethnicity	10 [0.4%]	6 [0.3%]	9 [0.4%]
Socioeconomic variables			
Civil status	167 [6.4%]	104 [5.3%]	162 [7.2%]
Qualifications	163 [6.2%]	106 [5.4%]	165 [7.3%]
Employment	162 [6.2%]	103 [5.3%]	161 [7.2%]
Car ownership	159 [6.1%]	99 [5.1%]	159 [7.0%]
Home ownership	163 [6.2%]	100 [5.1%]	162 [7.2%]
Clinical variables			
Primary renal disease	30 [1.1%]	22 [1.1%]	12 [0.5%]
Dialysis modality	13 [0.5%]	14 [0.7%]	16 [0.7%]
Previous transplant	12 [0.5%]	16 [0.8%]	14 [0.6%]
Comorbidity variables			
Obesity	418 [15.9%]	180 [9.2%]	124 [5.5%]
Diabetes	25 [1.0%]	22 [1.1%]	7 [0.3%]
Ischaemic heart disease	31 [1.2%]	23 [1.2%]	11 [0.5%]
Heart failure	33 [1.3%]	25 [1.3%]	10 [0.4%]
Atrial fibrillation	34 [1.3%]	23 [1.2%]	10 [0.4%]
Cardiac valve replacement	34 [1.3%]	23 [1.2%]	13 [0.6%]
Pacemaker	33 [1.3%]	24 [1.3%]	11 [0.5%]
Cerebrovascular disease	34 [1.3%]	25 [1.3%]	11 [0.5%]
Peripheral vascular disease	34 [1.3%]	23 [1.2%]	11 [0.5%]
Abdominal aortic aneurysm	35 [1.3%]	24 [1.3%]	11 [0.5%]
Chronic respiratory disease	33 [1.3%]	24 [1.3%]	10 [0.4%]
Liver disease	32 [1.2%]	27 [1.4%]	10 [0.4%]
Blood Borne Viruses	32 [1.2%]	24 [1.3%]	11 [0.5%]
Malignancy	29 [1.1%]	23 [1.2%]	10 [0.4%]
Mental Illness	31 [1.2%]	27 [1.4%]	10 [0.4%]
Dementia	33 [1.3%}	23 [1.2%]	12 [0.5%]
CCI Score	38 [1.5%]	30 [1.5%]	14 [0.6%]

3.3. Results

3.3.1. *Patient characteristics*

The baseline demographic, socioeconomic and clinical characteristics of the study population (n=6844) are presented in Table 3.3. The study population consisted of 2623 dialysis, 1959 waiting list and 2262 transplant patients. Compared with the waiting list and transplant populations, the dialysis population were significantly older, more predominantly male and a higher proportion had a primary renal diagnosis of diabetes or renal vascular disease. Dialysis patients were significantly less likely to have obtained qualifications at secondary or higher education level, and had lower rates of employment, car ownership and home ownership, suggesting they were a more socioeconomically deprived population compared with the waiting list and transplant populations. Compared with the transplant population, a significantly higher proportion of the waiting list population were female, from Black, Asian or Minority Ethnic (BAME) backgrounds and were divorced, separated or widowed. Significantly fewer patients on the waiting list had achieved qualifications at secondary or higher education level, were employed and owned a car or a house compared with the transplant population.

Table 3.3. Patient characteristics by cohort				
	Dialysis	**Waiting List**	**Transplant**	**p-value**
Demographic variables				
Median age (years)	58.4 [47.5 – 67.2]	51.1 [41.7 – 60.3]	50.3 [40.1 – 59.9]	<0.0001
Gender				<0.0001
Male	1703 [64.9%]	1135 [57.9%]	1421 [62.8%]	
Female	920 [35.1%]	824 [42.1%]	841 [37.2%]	
Ethnicity				<0.0001
White	2099 [80.3%]	1463 [74.9%]	1866 [82.8%]	
Asian	294 [11.3%]	242 [12.4%]	212 [9.4%]	
Black	185 [7.1%]	213 [10.9%]	140 [6.2%]	
Other	35 [1.3%]	35 [1.8%]	35 [1.6%]	
Socioeconomic variables				
Civil status				<0.0001
Married / Living with partner	1504 [61.2%]	1083 [58.4%]	1288 [61.3%]	
Divorced / Separated / Widowed	474 [19.3%]	329 [17.4%]	298 [14.2%]	
Single	478 [19.5%]	443 [23.9%]	514 [24.5%]	
Qualifications				<0.0001
Higher education level	396 [16.1%]	366 [19.8%]	469 [22.4%]	
Secondary education level	1016 [41.3%]	902 [48.7%]	1046 [49.9%]	
No qualifications	1048 [42.6%]	585 [31.6%]	582 [27.8%]	
Employment status				<0.0001
Employed	489 [19.9%]	644 [34.7%]	756 [36.0%]	
Unemployed	180 [7.3%]	163 [8.8%]	173 [8.2%]	
Long term sick / disability	775 [31.5%]	535 [28.8%]	595 [28.3%]	
Retired	908 [36.9%]	406 [21.9%]	420 [20.0%]	
Other	109 [4.4%]	108 [5.8%]	157 [7.5%]	
Car ownership	1754 [71.2%]	1444 [77.6%]	1765 [83.9%]	<0.0001
Home ownership	1327 [53.9%]	1043 [56.1%]	1321 [62.9%]	<0.0001
Clinical variables				
Primary renal diagnosis				<0.0001
Diabetic nephropathy	711 [27.4%]	238 [12.3%]	322 [14.3%]	
Glomerulonephritis	434 [16.7%]	432 [22.3%]	554 [24.6%]	
Polycystic kidney disease	212 [8.2%]	321 [16.6%]	333 [14.8%]	
Pyelonephritis	188 [7.3%]	230 [11.9%]	267 [11.9%]	
Hypertensive nephropathy	170 [6.6%]	119 [6.1%]	127 [5.6%]	
Renal vascular disease	91 [3.5%]	18 [0.9%]	39 [1.7%]	
Other	386 [14.9%]	310 [16.0%]	357 [15.9%]	
Uncertain	401 [15.5%]	269 [13.9%]	251 [11.2%]	
Dialysis modality				-
Haemodialysis	1843 [70.6%]	1166 [60.0%]	1163 [51.8%]	
Haemodiafiltration	221 [8.5%]	149 [7.7%]	54 [2.4%]	
CAPD	331 [12.7%]	160 [8.2%]	313 [13.9%]	
APD	215 [8.2%]	146 [7.5%]	214 [9.5%]	
Pre-dialysis	-	324 [16.7%]	478 [21.3%]	
Failing transplant	-	-	24 [1.1%]	
Previous transplant	300 [11.5%]	514 [26.5%]	294 [13.1%]	<0.0001

Data are median [IQR] or number [%]. Some data were missing and excluded from percentage calculations, numbers of missing data are shown in Table 3.2. Kruskal-Wallis test for age. All others chi-squared test. CAPD; Continuous ambulatory peritoneal dialysis, APD; Automated peritoneal dialysis

3.3.2. Comorbidity prevalence

The prevalence of comorbidity amongst the 3 cohorts is shown in Table 3.4. Overall the most common comorbidity was diabetes, followed by obesity and ischaemic heart disease. The dialysis population had a significantly higher prevalence of most of the studied comorbidities compared with the waiting list and transplant populations, with the exception of cardiac valve replacements, blood borne viruses and dementia. There were no significant differences in the prevalence of comorbidities between the waiting list and transplant cohorts. In the dialysis population, 40.3% patients had a CCI score of 0, compared with 65.9% of the waiting list population and 67.3% of the transplant population.

Table 3.4. Prevalence of comorbidity by cohort

	Dialysis	Waiting List	Transplant	p-value
Diabetes	1074 [41.3]	344 [17.7]	437 [19.4]	<0.0001
Ischaemic heart disease	534 [20.6]	179 [9.3]	193 [8.6]	<0.0001
Heart failure	193 [7.5]	60 [3.1]	57 [2.6]	<0.0001
Atrial fibrillation	113 [4.4]	48 [2.5]	37 [1.6]	<0.0001
Cardiac valve replacement	31 [1.2]	27 [1.4]	19 [0.8]	0.2
Pacemaker	40 [1.5]	16 [0.7]	14 [0.7]	0.005
Cerebrovascular disease	238 [9.2]	104 [5.4]	111 [4.9]	<0.0001
Peripheral vascular disease	234 [9.0]	69 [3.6]	74 [3.3]	<0.0001
Abdominal aortic aneurysm	44 [1.7]	6 [0.3]	6 [0.3]	<0.0001
Chronic respiratory disease	315 [12.2]	138 [7.1]	175 [7.8]	<0.0001
Chronic liver disease	67 [2.6]	25 [1.3]	44 [2.0]	0.009
Blood borne viruses	70 [2.7]	62 [3.2]	51 [2.3]	0.2
Malignancy	346 [13.3]	135 [7.0]	145 [6.4]	<0.0001
Mental illness	225 [8.7]	141 [7.3]	133 [5.9]	0.001
Dementia	8 [0.3]	5 [0.3]	3 [0.1]	0.4
Obesity	716 [32.5]	372 [20.9]	439 [20.5]	<0.0001
CCI Score				<0.0001
0	1042 [40.3%]	1271 [65.9%]	1513 [67.3%]	
1	500 [19.3%]	288 [14.9%]	365 [16.2%]	
2	488 [18.9%]	258 [13.4%]	229 [10.2%]	
≥3	555 [21.5%]	112 [5.8%]	141 [6.3%]	

Data are number [%]

Some data were missing and excluded from percentage calculations, numbers of missing data are shown in Table 3.2.

3.3.3. Comorbidity by centre

To compare the overall burden of comorbidity of patients between centres, the proportion of dialysis, waiting list and transplant patients with a CCI score of 2 or more in each centre were compared (Table 3.5. and Figure 3.1). There was significant inter-centre variation in the proportion of patients with a CCI score of 2 or more for patients on dialysis (range 21.2% – 50.0%, p=0.002), patients on the waiting list (range 11.5% – 36.2%, p=0.025) and transplanted patients (range 7.6% – 27.6%, p=0.008). One centre (Coventry) was excluded from this calculation due to the low number of patients recruited. As expected, the proportion of patients with a CCI score of 2 or more was higher

in the dialysis population than in the waiting list and transplant populations in all centres. The proportion of patients with a CCI score of 2 or more tended to be similar between centres' transplant and waiting list populations, except in 2 centres where the waiting list population had a significantly higher burden of comorbidity than the transplant population (Plymouth and Cardiff).

Table 3.5. Proportion of patients with CCI score ≥ 2

	Dialysis		Waiting list		Transplant	
CENTRE	n	%	n	%	n	%
Belfast	45	48.4	14	18.4	14	18.0
Birmingham	142	37.9	28	21.7	23	19.0
Bristol	43	32.1	13	16.1	15	14.6
Cambridge	84	49.4	29	16.6	36	18.8
Cardiff	35	46.7	25	36.2	22	21.4
Edinburgh	44	50.0	14	19.4	20	20.2
Glasgow	45	38.8	27	29.7	27	27.6
Leeds	20	36.4	19	20.9	15	14.0
Leicester	36	50.0	9	20.9	9	20.9
Liverpool	108	46.0	24	21.6	14	12.6
London – Bart's	38	32.8	8	13.8	9	13.0
London – Guy's	58	43.3	24	15.0	30	14.9
London – Royal Free	14	21.2	12	15.8	14	17.7
London – St George's	67	35.3	18	17.7	10	10.8
London – West	55	38.2	15	20.0	20	22.0
Manchester	32	39.5	14	13.0	12	7.6
Newcastle-upon-Tyne	30	48.4	16	20.8	12	12.8
Nottingham	25	39.7	10	16.7	14	21.9
Oxford	5	21.7	22	21.4	33	22.6
Plymouth	14	45.2	9	33.3	5	12.5
Portsmouth	40	37.7	9	11.5	8	10.4
Sheffield	63	40.9	9	16.7	6	10.9
p-value	**0.002**		**0.025**		**0.008**	

Coventry not included due to insufficient numbers

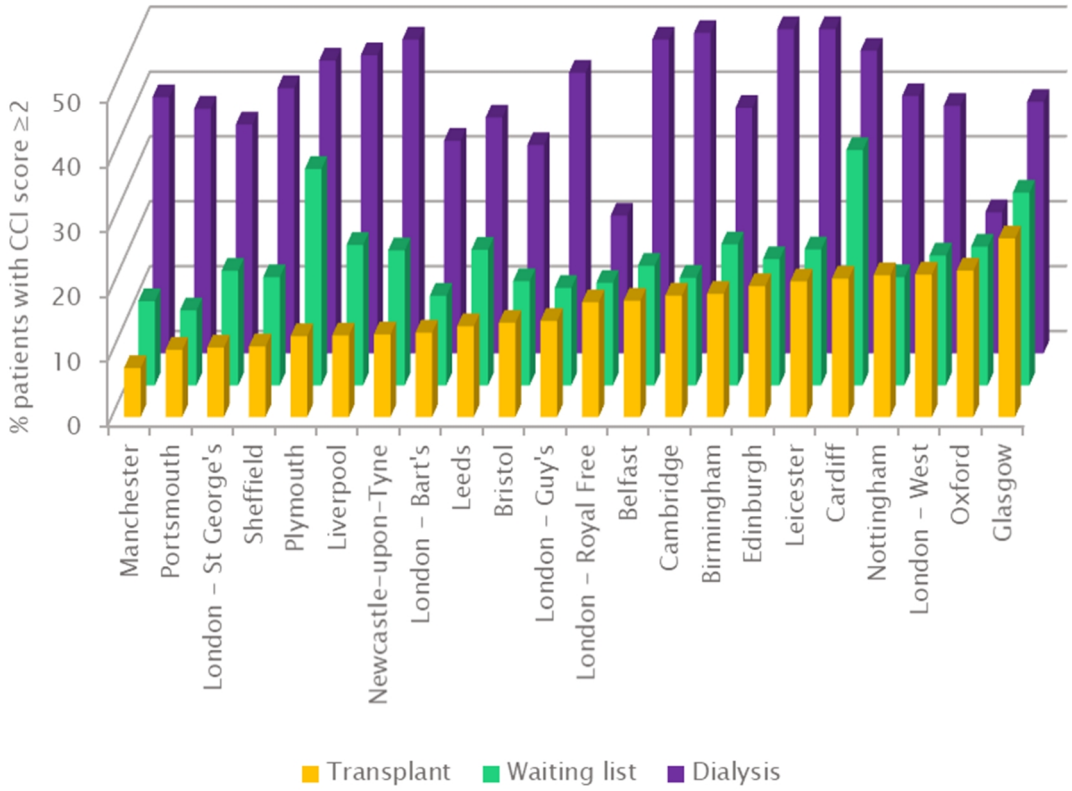

Figure 3.1. Proportion of patients with CCI score ≥ 2 by centre and by cohort. Graph is ordered from left to right by increasing proportion of transplant patients with CCI score ≥ 2.

The proportion of patients with the three most prevalent comorbidities (diabetes, obesity and ischaemic heart disease) in each cohort and at each centre were also compared. In each analysis one centre (Coventry) was excluded due to the low number of patients recruited from this centre.

Figure 3.2. and Table 3.6. compare the proportion of patients with diabetes in each cohort at each centre. There was no significant difference between centres in the proportion of dialysis patients with diabetes (range 32.1% - 50.0%, p=0.691), however there was significant inter-centre variation in the proportion of listed patients (range 7.8% - 34.0%, p=0.0001) and transplanted

patients (range 9.4% - 44.5%, p<0.0001) who had diabetes. The proportion of patients with diabetes was highest in the dialysis population across all centres. In general, the waiting list and transplant populations in each centre had similar rates of diabetes. There were two notable exceptions to this rule (Plymouth and Leicester) where the waiting list population comprised of around 14% more diabetics than the transplant population. Another anomaly is the centre of Oxford, where the rate of diabetes in transplanted patients (44.5%) and listed patients (34%) was significantly higher than in all other centres.

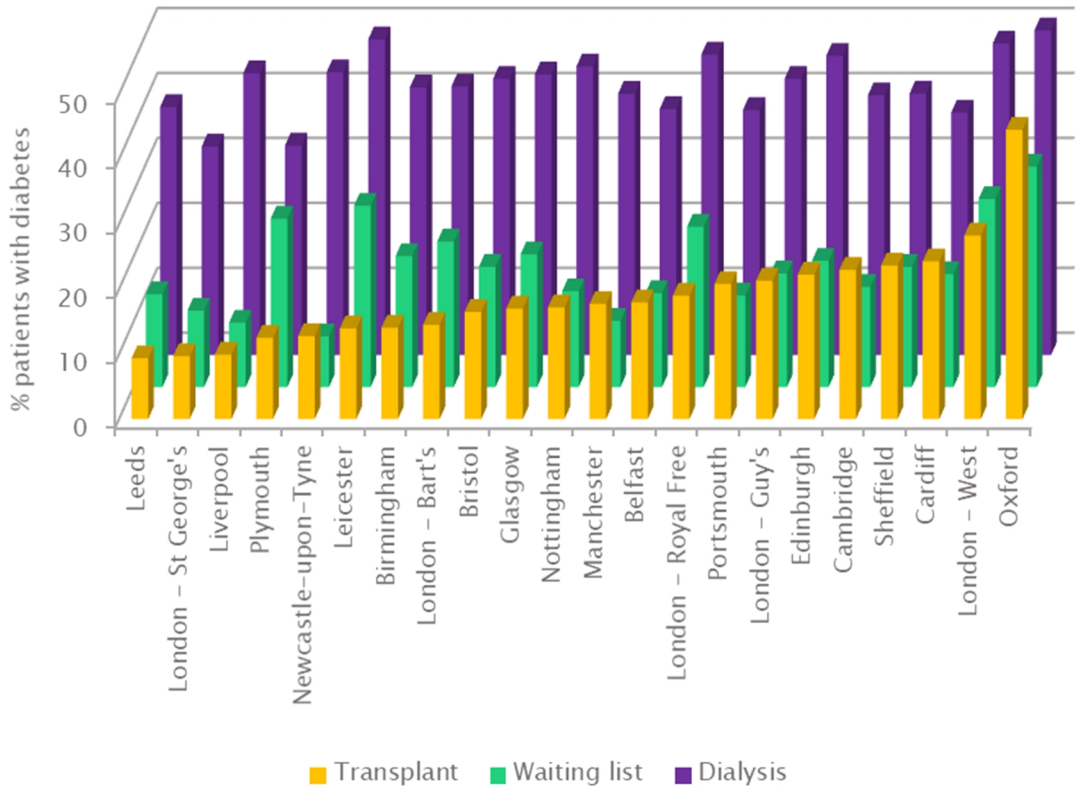

Figure 3.2. Proportion of patients with diabetes by centre and by cohort.
Graph is ordered from left to right by increasing proportion of transplant patients with diabetes.

Table 3.6. Proportion of patients with diabetes

	Dialysis		Waiting list		Transplant	
CENTRE	n	%	n	%	n	%
Belfast	36	37.9	11	14.5	14	18.0
Birmingham	155	41.2	26	20.2	17	14.1
Bristol	57	42.5	15	18.5	17	16.5
Cambridge	68	40.0	27	15.4	45	23.0
Cardiff	28	37.3	12	17.4	25	24.3
Edinburgh	41	46.1	14	19.4	22	22.2
Glasgow	51	43.2	19	20.4	17	17.0
Leeds	21	38.2	13	14.3	10	9.4
Leicester	35	48.6	12	27.9	6	14.0
Liverpool	102	43.4	11	9.9	11	9.9
London – Bart's	48	41.4	13	22.4	10	14.5
London – Guy's	57	42.5	28	17.5	43	21.3
London – Royal Free	31	46.3	19	24.7	15	19.0
London – St George's	61	32.1	12	11.8	9	9.7
London – West	71	48.0	22	29.0	26	28.3
Manchester	33	40.2	11	10.2	28	17.7
Newcastle-upon-Tyne	27	43.6	6	7.8	12	12.8
Nottingham	28	44.4	9	14.8	11	17.2
Oxford	12	50.0	36	34.0	65	44.5
Plymouth	10	32.3	7	25.9	5	12.5
Portsmouth	40	37.7	11	14.1	16	20.8
Sheffield	62	40.3	10	18.5	13	23.6
p-value	**0.691**		**0.0001**		**<0.0001**	

Coventry not included due to insufficient numbers

The proportion of patients with obesity in each cohort in each centre is shown in Table 3.7. and Figure 3.3. There was no significant inter-centre variation in the proportion of patients with obesity for the dialysis cohort (range 20.3% - 41.7%, p=0.354), the waiting list cohort (range 12.1% - 33.3%, p=0.146) and the transplant cohort (range 12.7% - 31.0%, p=0.230).

Table 3.7. Proportion of patients with obesity

	Dialysis		Waiting list		Transplant	
CENTRE	n	%	n	%	n	%
Belfast	30	38.0	18	24.0	14	18.0
Birmingham	86	32.3	25	21.6	26	21.7
Bristol	33	35.1	11	15.5	15	16.9
Cambridge	47	28.5	28	16.4	30	15.6
Cardiff	17	39.5	18	33.3	28	29.8
Edinburgh	27	32.1	7	12.1	15	16.7
Glasgow	38	41.3	20	24.4	20	20.8
Leeds	18	34.0	24	26.1	19	18.6
Leicester	20	28.2	12	28.6	7	16.3
Liverpool	81	35.1	25	22.7	27	24.6
London – Bart's	25	30.1	8	15.4	8	12.7
London – Guy's	43	34.1	34	21.7	32	16.4
London – Royal Free	13	20.3	15	20.0	17	21.3
London – St George's	49	29.2	15	15.2	17	18.5
London – West	31	24.4	10	14.7	13	17.3
Manchester	26	40.6	19	22.4	35	24.7
Newcastle-upon-Tyne	16	25.8	12	15.6	22	23.4
Nottingham	18	30.5	10	16.7	15	23.4
Oxford	5	35.7	21	24.7	34	24.6
Plymouth	5	41.7	2	14.3	9	31.0
Portsmouth	37	37.8	19	26.0	18	23.7
Sheffield	51	34.5	16	31.4	16	29.6
p-value	**0.354**		**0.146**		**0.230**	

Coventry not included due to insufficient numbers

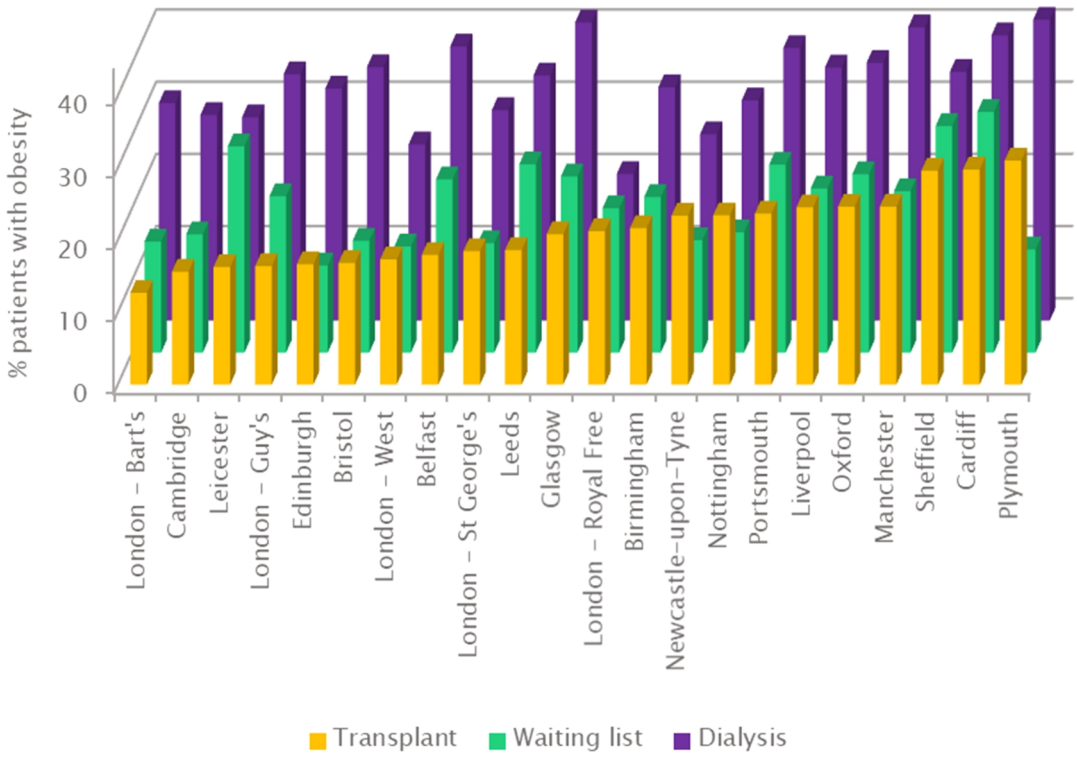

Figure 3.3. Proportion of patients with obesity by centre and by cohort.
Graph is ordered from left to right by increasing proportion of transplant patients with obesity.

The proportion of patients with ischaemic heart disease in each cohort and in each centre is shown in Table 3.8. and Figure 3.4. There was no significant inter-centre variation in the proportion of patients with ischaemic heart disease for the waiting list cohort (range 3.8% - 16.1%, p=0.185), but the proportion of patients with ischaemic heart disease was significantly different between centres for the dialysis (range 10.6% - 35.2%, p=0.0003) and the transplant cohorts (range 0% - 23.9%, p<0.0001).

Table 3.8. Proportion of patients with ischaemic heart disease

	Dialysis		Waiting list		Transplant	
CENTRE	n	%	n	%	n	%
Belfast	24	25.5	9	11.8	12	15.4
Birmingham	76	20.3	9	7.0	6	5.0
Bristol	15	11.2	9	11.1	4	3.9
Cambridge	43	25.3	16	9.1	14	7.3
Cardiff	12	16.0	9	13.0	11	10.7
Edinburgh	17	19.1	6	8.2	8	8.1
Glasgow	33	27.7	15	16.1	17	17.2
Leeds	10	18.2	7	7.7	7	6.5
Leicester	16	22.2	5	11.6	3	7.0
Liverpool	58	24.7	10	9.0	6	5.4
London – Bart's	17	14.7	3	5.2	2	2.9
London – Guy's	27	20.2	6	3.8	21	10.4
London – Royal Free	7	10.6	4	5.2	8	10.0
London – St George's	29	15.3	11	10.8	7	7.5
London – West	51	35.2	12	16.0	22	23.9
Manchester	14	17.1	6	5.6	3	1.9
Newcastle-upon-Tyne	12	19.4	8	10.4	10	10.6
Nottingham	9	14.3	5	8.3	6	9.4
Oxford	5	21.7	14	13.2	16	11.0
Plymouth	9	29.0	3	11.1	2	5.0
Portsmouth	20	18.9	8	10.3	8	10.4
Sheffield	30	19.5	3	5.6	0	0.0
p-value	**0.0003**		**0.185**		**<0.0001**	

Coventry not included due to insufficient numbers

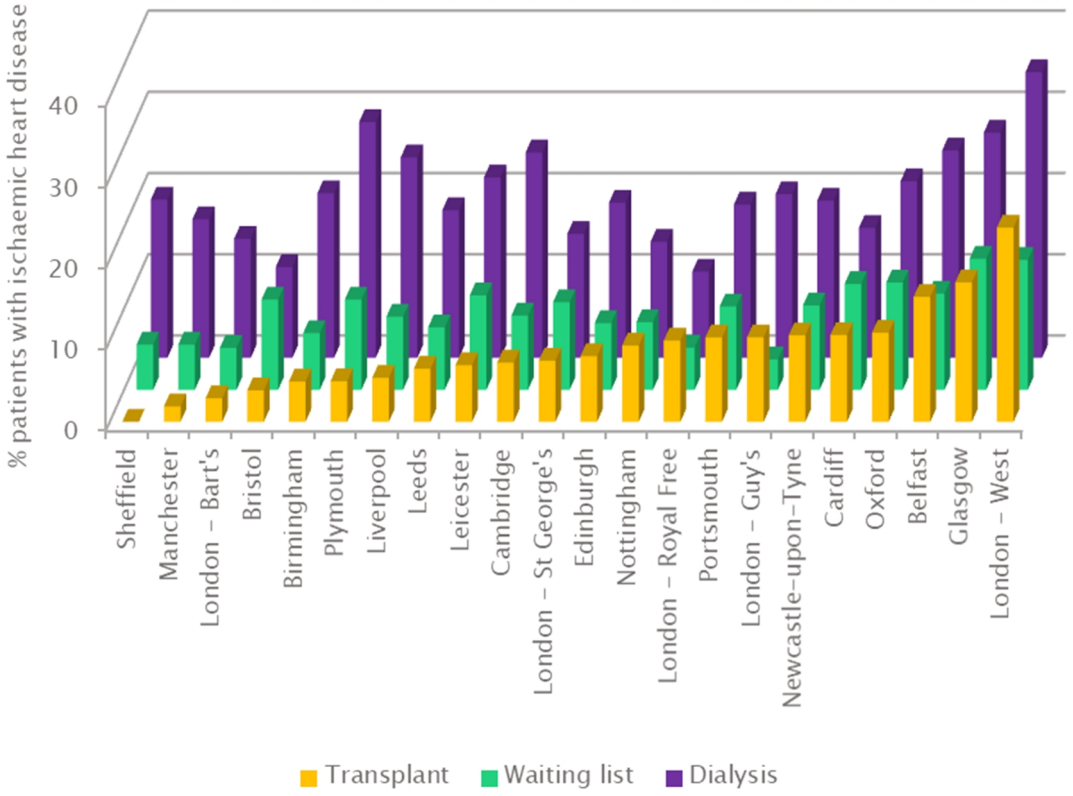

Figure 3.4. Proportion of patients with ischaemic heart disease by centre and by cohort.
Graph is ordered from left to right by increasing proportion of transplant patients with ischaemic heart disease.

3.4. Discussion

This analysis has showed for the first time that the comorbidity burden of dialysis, waiting list and transplant patients differs significantly between kidney transplant centres in the UK. These results provide two potential explanations for previously reported centre differences in the proportion of patients listed for and receiving a kidney transplant.[3-5] First, the fact that each centre serves a dialysis population with significantly different levels of comorbidity, means that centres with sicker patient populations may have justifiably lower listing and transplantation rates. Secondly, our findings suggest that the comorbidity burden of listed and transplanted patients also differs significantly between centres, implying variable acceptance criteria and risk tolerance which may be contributing to inequity in access to kidney transplantation.

The findings of this study highlight the importance of adjusting for comorbidity in any future analyses comparing patient outcomes between centres, as comorbidity is likely to be a significant confounding factor. Furthermore, the demonstrated differences in case-mix between centres may enable improved allocation of resources and planning of services to better match patient population needs.

The strengths of this study are that for the first time we have presented prospectively collected accurate comorbidity data for large national cohorts of dialysis, waiting list and transplant patients in the UK. The UKRR previously reported comorbidity data for UK adult incident RRT patients in

2014,[115] however data was complete for only 55.7% of patients. In the present study a maximum of 10% of data were missing for any comorbidity variable, with the majority of variables only missing around 1% data. Furthermore, UKRR only collected comorbidity data for patients starting dialysis or receiving a pre-emptive transplant and did not examine the prevalence of comorbidity amongst waiting-list or transplant populations. The main limitation of this study is the potential for selection bias, as we were unable to recruit the entire UK ESRD population. However, we recruited around two-thirds of all dialysis, waiting list and transplant patients from the study era and included patients from all UK renal units in order to minimise bias. Unfortunately, patient numbers were too small for 1 centre which had to be excluded from the analysis.

Our data highlighted striking differences between dialysis, waiting list and transplant patients. Dialysis patients had significantly lower levels of educational attainment, employment, car ownership and house ownership compared with waiting list and transplant patients. Interestingly, the same socioeconomic factors were also less common in waiting list patients when compared with transplant patients. This is in keeping with previous studies showing that socioeconomic deprivation acts as an important factor in access to transplantation in the UK.[4, 5, 116-118] The dialysis population in our study were significantly older and had a higher comorbidity burden than the waiting list and transplant populations. Age and comorbidity are recognised barriers to selection for transplantation,[42, 119, 120] but our results suggest that comorbidity may be interpreted differently during the assessment of transplant suitability, between centres in the UK.

The finding that dialysis populations in different centres had significantly different levels of comorbidity is not surprising. However, the assessment process for determining a patient's suitability for transplantation should be uniform between centres and lead to selection of a group of patients with comparable comorbidity burden. Our results suggest that some centres are listing and transplanting patients with significantly higher comorbidity than others. The rate of diabetes, obesity, ischaemic heart disease and a modified CCI of 2 or more among listed and transplanted patients, differed between centres by up to 35%. In most centres, the comorbidity burden of the waiting list cohort was largely similar to that of the transplant cohort. However, in a few specific centres there appeared to be a pattern where the waiting list population had a significantly higher level of comorbidity than the transplant population, perhaps signifying a further selection process between listing and transplantation. Interestingly, a few centres consistently had the highest rates of comorbidity among their transplant populations. Oxford and Cardiff were in the top five centres with the highest rates of comorbidity for all of the conditions analysed (diabetes, obesity, ischaemic heart disease and a CCI of two or more). Similarly, London West was in the top five centres for three of the analyses (diabetes, ischaemic heart disease and a CCI of two or more), and Glasgow for two of the analyses (ischaemic heart disease and a CCI of two or more). This does suggest that specific centres may have a higher risk tolerance with regards to transplantation and comorbidity. Within the scope of this study we were unable to explore the reasons for the demonstrated centre differences. It is plausible that centres with sicker dialysis populations would be more likely to accept higher risk patients for kidney transplantation. However, the results of this study showed that this was not the case; the

comorbidity burden of centres' dialysis populations did not correlate with that of their waiting list and transplant populations. A previous study reported considerable variation in the assessment processes and exclusion criteria for transplantation between UK renal transplant centres based on the responses of nephrologists, surgeons and transplant coordinators to a questionnaire.[6] Differences in centre practices in determining patient suitability for transplantation may depend on the experience of clinical staff and local availability of resources.

It is known that survival rates following kidney transplantation are comparable between centres in the UK.[121] Therefore, centres transplanting patients with higher comorbidity have not been shown to have inferior outcomes. It could be argued that more selective and risk-averse centres may be disadvantaging some patients who could benefit from good outcomes from transplantation and could expand their selection criteria to include such patients. However, further work is needed to analyse the effect of comorbidity on the outcomes of dialysis and transplanted patients in the UK. Patient selection for transplantation should be fair, transparent and based on validated criteria, and should not be affected by the centre that a patient is seen in. The development of an individualised survival prediction tool for ESRD patients would provide a more objective and evidence-based guide to treatment decisions and could be used to implement national selection criteria in order to standardise access to kidney transplantation in the UK.

CHAPTER 4

Access to Living Donor Kidney Transplantation

4.1. Introduction

It is now widely acknowledged that living donor kidney transplantation (LDKT) provides better clinical outcomes than deceased donor kidney transplantation (DDKT).[18, 19, 122] Kidneys from living donors are generally healthier and have not been exposed to the detrimental effects of brain death, circulatory death or prolonged periods of ischaemia. UK transplant registry data show that patient and graft survival rates are consistently higher for LDKT than DDKT (Table 4.1). This is despite significantly poorer levels of human leukocyte antigen (HLA) matching (26% level 4 matches [1DR + 2B mismatches or 2DR mismatches] in LDKT compared to 6% in DDKT).[13]

Table 4.1. Patient and graft survival rates for kidney transplantation in the UK

	Patient survival (%)			Graft survival (%)		
	1 year	5 year	10 year	1 year	5 year	10 year
Living donor	99	94	91	97	92	82
Donor after brain death	96	88	76	93	87	76
Donor after circulatory death	95	85	72	93	86	76

Includes adult transplants performed between 1 April 2004 – 31 March 2006. Data from NHS Blood and Transplant.[13]

LDKT also provides more timely access to transplantation. The elective LDKT procedure can be scheduled without delay and can be performed at a time when both donor and recipient health is optimal. Currently, the median waiting time for DDKT in the UK is 2 years.[14] LDKT enables patients to avoid the long waiting list for DDKT, and thereby minimises the exposure to pre-transplant dialysis and its associated morbidity. LDKT provides the more likely prospect of avoiding dialysis entirely, through pre-emptive transplantation. Evidence shows that time on dialysis prior to transplantation

confers a considerable dose-dependent negative impact on post-transplant outcomes and is considered by many to be the most important modifiable risk factor in transplant outcomes.[19, 20, 123] Avoidance of dialysis also makes pre-emptive transplantation the most cost-effective treatment option for patients with end-stage renal disease (ESRD).[124] In 2018, the rate of pre-emptive transplantation in the UK was 16.5% for DDKT and 40.2% for LDKT.[13]

UK Renal Association guidelines recommend that LDKT be considered the treatment of choice for all patients suitable for kidney transplantation, whenever an appropriate living donor is available.[125] The guidelines also highlight the fact that pre-emptive LDKT should be the optimal treatment strategy.

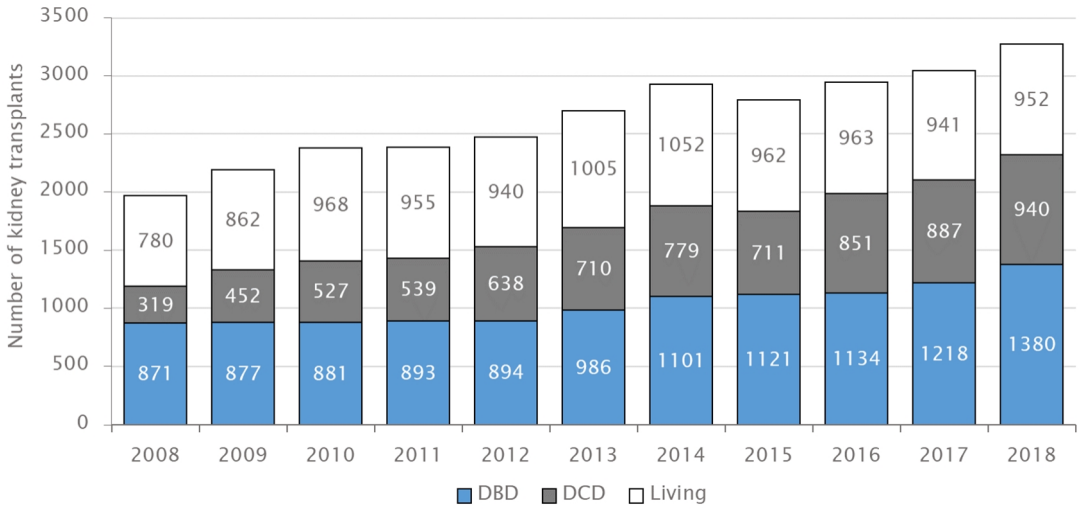

Figure 4.1. Number of adult kidney transplants by donor type (Source: NHS Blood and Transplant annual report on kidney transplantation 2008–2018)[14]

Despite the numerous advantages of LDKT, currently only around one third of kidney transplants undertaken in the UK are from living donors (Figure

4.1). Concerningly, LDKT numbers have fallen by 9.5% since 2014, but this has corresponded with an increase in the number of DDKTs. Of 74 countries submitting data on LDKT to the International Registry on Organ Donation and Transplantation (IRODaT) in 2017,[15] the UK ranked 14th for number of LDKTs per million population (pmp) (Figure 4.2). The UK rate of 15 transplants pmp is only around half that of the best performing countries. It is important to bear in mind that a country's LDKT rate is influenced by the DDKT rate and that many of these top performing countries do not have an established deceased donor programme. However, several countries with successful LDKT and DDKT programmes still have a higher LDKT rate than the UK, such as the Netherlands, Israel, South Korea, USA, Denmark, New Zealand and Switzerland, suggesting substantial scope for further expansion of the UK living donor pool.

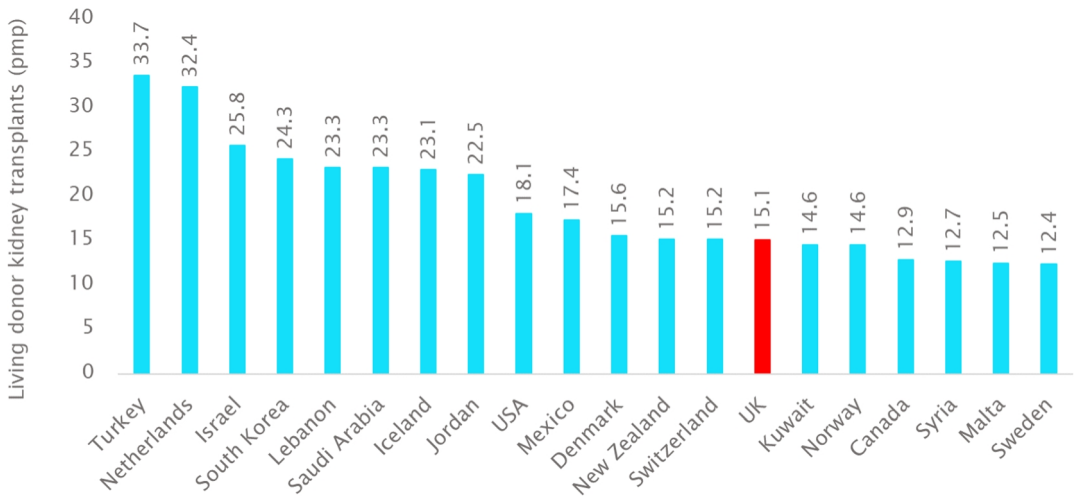

Figure 4.2. Top 20 countries for number of living donor kidney transplants per million population (pmp) 2017 (Source: International Registry on Organ Donation and Transplantation (IRODaT)[15])

Improving LDKT activity has been recognised as a major priority for transplantation in the UK. A strategy set out by NHS Blood and Transplant (NHSBT) in 2014 aims to increase the LDKT rate to 26 transplants pmp by 2020.[21] The key objectives of the strategy are to increase LDKT activity whilst maintaining donor safety and welfare, ensure all suitable recipients have equity of access to LDKT, embed the principle of "transplant first" as best clinical practice across the UK and expand the National Living Donor Kidney Sharing Schemes. However, with the current UK LDKT rate static at 15 pmp there is significant progress to be made. There are limited data on the factors that may inhibit or facilitate patients to receive a LDKT or a pre-emptive LDKT in the UK. A better understanding of these factors is vital to enable identification of target patient groups and aid the development of appropriate interventions to improve LDKT rates. The aim of this analysis was to investigate the factors influencing access to LDKT in the UK. The principle objectives were to examine a national sample of UK kidney transplant recipients to identify the recipient characteristics associated with achieving LDKT compared with DDKT, and also to investigate whether any recipient variables were associated with receiving pre-emptive LDKT versus LDKT after the initiation of dialysis.

4.2. Methods

4.2.1. Study population

This analysis included kidney transplant recipients from the incident transplant cohort of ATTOM (n=2262). Patients were recruited at the time of transplantation from all 23 UK transplant centres. In each centre, recruitment took place over a 12-month period between 1 November 2011 and 31 March 2013. Patients aged 18 – 75 years were eligible for recruitment. For full details about patient recruitment methods please see Chapter 2. For the purposes of this analysis, patients undergoing simultaneous pancreas-kidney transplants (n=150) and other multi-organ transplants (n=12) were excluded. Thus, the final study population included 2100 kidney-only transplant recipients. The study population represented 73.2% of patients in the national kidney-only transplant population who were eligible for recruitment to the study (Figure 4.3).

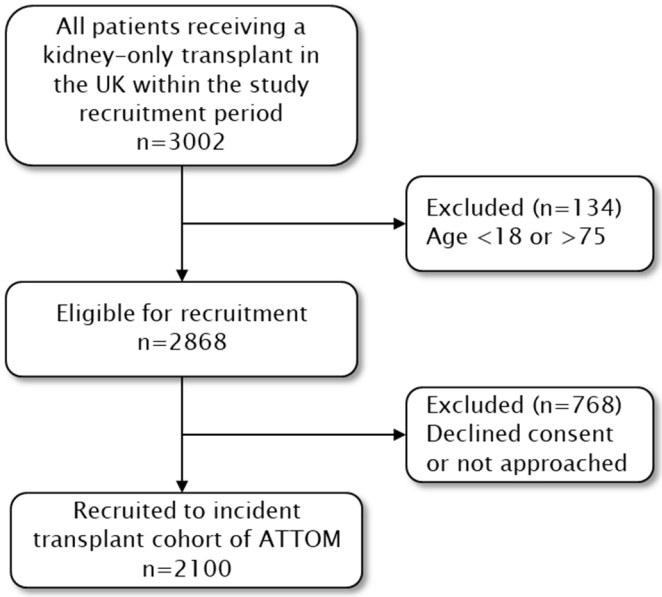

Figure 4.3. Study population

4.2.2. Data variables

Baseline demographic, socioeconomic, clinical, comorbidity and transplant data were collected for each patient at the time of transplantation (Appendix A.2.). The predictor variables of interest in this analysis included:

(a) demographic variables: age, gender, ethnicity, country

(b) socioeconomic variables: civil status, highest qualification, employment status, car ownership, home ownership, health literacy, first language, country of birth

(c) clinical variables: primary renal disease, modified Charlson Comorbidity Index (CCI), body mass index (BMI), smoking status, previous transplantation, sensitisation level

Variable definitions are given in Appendix A.3. For the purposes of this analysis, recipient age was divided into the following groups: 18-34, 35-49, 50-64 and 65-75 years. Patients were classified by the country in which they underwent transplantation. Civil status was divided into 3 groups; married or living with partner, divorced or separated or widowed and single. Health literacy was assessed by a single item screening question: "How often do you need help to read instructions, leaflets or other written material from your doctor or pharmacy?". Answers of "Never" or "Rarely" were recorded as normal health literacy, and answers of "Sometimes", "Often" or "Always" were recorded as limited health literacy. A modified Charlson Comorbidity Index (CCI) designed specifically for patients with ESRD was calculated for each patient using the methods described in Chapter 2. In order to reduce the number of degrees of freedom, the modified CCI was used during modelling

rather than considering each comorbidity variable separately. This allowed more factors to be considered in the model. The modified CCI was divided into 4 groups; 0, 1, 2 and ≥3. BMI was grouped in accordance with the World Health Organisation (WHO) BMI classifications of Underweight (<18.5 kg/m^2), Normal (18.5 - 24.9 kg/m^2), Overweight (25.0 - 29.9 kg/m^2) and Obese (≥30.0 kg/m^2).[126] Highly sensitised patients were defined as those with a calculated reaction frequency (cRF) of more than 85%, as per the NHSBT definition.[79]

4.2.3. Statistical methods

Baseline characteristics of LDKT and DDKT recipients and donors were presented as numbers with percentages (%) compared by chi-squared tests for categorical data and medians with interquartile ranges (IQR) compared with Wilcoxon tests for non-parametric continuous data.

The primary outcome measure was the type of transplant received. Recipient variables associated with receiving LDKT versus DDKT were analysed using logistic regression. A manual backward elimination method was used to build the multivariable model. Variables leading to a change in log likelihood at $p<0.15$ on univariable analysis were entered into the multivariable model. The importance of each variable in the model was then tested by examining the difference in log-likelihood between the model with and without the variable. If the difference was not significant ($p>0.05$) on likelihood ratio test, the variable was removed. Each time a variable was removed, the effect of removing each of the remaining variables was retested until the most parsimonious model was achieved. Continuous variables were explored as linear, fractional polynomials and categorical variables. Potential interactions

between variables were tested; none were significant. Correlation between categorical variables was tested using Cramer's V correlation coefficient, with values >0.15 considered to show strong correlation.[127]

The proportion of missing values did not exceed 10% for any variable (Table 4.2). For modelling purposes, missing values were imputed using the fully conditional specification logistic regression method. Ten imputed datasets were modelled separately, then combined to produce final parameter estimates. Sensitivity analysis using case-wise deletion of missing values did not change conclusions.

Complex links between socioeconomic deprivation and ethnicity with respect to access to and outcomes from renal replacement therapy (RRT) have previously been reported.[128, 129] To avoid any confounding and/or interaction from ethnicity, a subgroup analysis was undertaken in White patients only, using the same multivariable modelling methods as described above.

A second subgroup analysis examined the recipient variables associated with receiving a transplant pre-emptively versus after the initiation of dialysis in the LDKT cohort. Multivariable modelling methods were the same as described above.

All data were analysed using SAS®9.4 (SAS Institute Inc, Cary, USA).

Table 4.2. Missing data	
Variable	n [%]
Recipient age	0 [0]
Recipient gender	0 [0]
Recipient ethnicity	4 [0.2]
Recipient country of residence	0 [0]
Recipient civil status	148 [7.1]
Recipient qualifications	149 [7.1]
Recipient employment status	145 [6.9]
Recipient car ownership	143 [6.8]
Recipient home ownership	146 [7.0]
Recipient health literacy	146 [7.0]
Recipient first language	141 [6.7]
Recipient country of birth	141 [6.7]
Recipient primary renal disease	6 [0.3]
Recipient modified CCI	8 [0.4]
Recipient BMI	106 [5.1]
Recipient smoking status	201 [9.6]
Recipient previous transplant	11 [0.5]
Recipient sensitisation level	0 [0]
Recipient pre-transplant treatment modality	11 [0.5]
Donor age	0 [0]
Donor gender	1 [0.1]
Donor ethnicity	19 [0.9]
Donor relationship	8 [0.4]

4.3. Results

4.3.1. Study population characteristics

As shown in Figure 4.3, the study population represented 73.2% of all patients undergoing kidney-only transplantation in the UK during the study recruitment period who were eligible for recruitment to the study. The chi-square goodness of fit test was used to compare the patient demographics of the national adult kidney-only transplant population (n=2868) and those who were recruited to the study (n=2100) (Table 4.3). There were no significant demographic differences, indicating that the study population was a nationally representative sample for the recruitment time period.

Table 4.3. Patient demographics of kidney-only transplant recipients – national population versus study population

Variable	National kidney-only transplant population (%)	ATTOM kidney-only transplant population (%)	p-value
Age group			0.714
18 – 34	16.6	17.2	
35 – 49	29.7	30.1	
50 – 64	37.9	37.9	
65 – 75	15.7	14.9	
Gender			0.480
Male	62.3	63.0	
Female	37.7	37.0	
Ethnicity			0.188
White	80.3	82.4	
Asian	10.9	9.6	
Black	6.6	6.2	
Other	1.8	1.6	
Missing	0.3	0.2	
Type of transplant			0.164
Living donor	37.2	38.7	
Deceased donor	62.8	61.3	

Of the 2100 kidney-only transplant recipients in the study, 1288 (61.3%) underwent DDKT and 812 (38.7%) underwent LDKT. There were considerable differences in the characteristics of LDKT and DDKT recipients (Table 4.4 and 4.5). LDKT recipients were significantly younger (median age 46 vs 54 years) and a higher proportion were of White ethnicity (87.1% vs 79.7%) and married or living with a partner (65.1% vs 60.2%). Compared with DDKT recipients, a higher proportion of LDKT recipients had achieved secondary education level qualifications (52.9% vs 47.1%), higher education level qualifications (27.2% vs 19.0), employment (43.4% vs 31.5%), car-ownership (91.0% vs 80.4%) and home-ownership (66.1% vs 62.5%), indicating they were a less socioeconomically deprived population. LDKT recipients were more likely to have normal health literacy (92.4% vs 86.6%), English as a first language (91.1% vs 86.3%) and to have the UK as their country of birth (87.2% vs 79.1%). There was a significantly lower prevalence of overall comorbidity and of diabetes, polycystic kidney disease, hypertension and renal vascular disease as the primary cause of renal failure in the LDKT group. A significantly higher proportion of LDKT recipients received pre-emptive transplants compared with DDKT recipients (35.7% vs 12.2%, $p<0.0001$). For patients who did undergo dialysis, the median time spent on dialysis before transplantation was 1.57 years for LDKT and 3.4 years for DDKT ($p<0.0001$).

Table 4.4. Kidney transplant recipient sociodemographic characteristics			
	LDKT recipients n=812	DDKT recipients n=1288	p-value
Median age (years)	46 [34 – 56]	54 [44 – 63]	<0.0001
Age group			<0.0001
18 – 34	229 [28.2]	132 [10.3]	
35 – 49	263 [32.4]	369 [28.7]	
50 – 64	252 [31.0]	543 [42.2]	
65 – 75	68 [8.4]	244 [18.9]	
Gender			0.267
Male	500 [61.6]	824 [64.0]	
Female	312 [38.4]	464 [36.0]	
Ethnicity			0.0002
White	707 [87.1]	1023 [79.7]	
Asian	62 [7.6]	140 [10.9]	
Black	35 [4.3]	96 [7.5]	
Other	8 [1.0]	25 [2.0]	
Civil status			<0.0001
Married / Living with partner	497 [65.1]	715 [60.2]	
Divorced / Separated / Widowed	68 [8.9]	210 [17.7]	
Single	199 [26.1]	263 [22.1]	
Qualifications			<0.0001
Higher education level	208 [27.2]	225 [19.0]	
Secondary education level	446 [58.4]	657 [55.4]	
No qualifications	110 [14.4]	305 [25.7]	
Employment status			<0.0001
Employed	332 [43.4]	375 [31.5]	
Unemployed	59 [7.7]	94 [7.9]	
Long term sick / disability	184 [24.1]	352 [29.6]	
Retired	115 [15.0]	297 [25.0]	
Other	75 [9.8]	72 [6.1]	
Car ownership	695 [91.0]	959 [80.4]	<0.0001
Home ownership	504 [66.1]	744 [62.5]	0.107
Health literacy			<0.0001
Normal	706 [92.4]	1030 [86.6]	
Limited	58 [7.6]	160 [13.5]	
English is first language	698 [91.1]	1029 [86.3]	0.001
Born in UK	668 [87.2]	944 [79.1]	<0.0001

Data are median [IQR] or number [%]. Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Table 4.2.
p-value derived from Wilcoxon test for median age. All others chi-squared test.

Table 4.5. Kidney transplant recipient clinical characteristics			
	LDKT recipients n=812	DDKT recipients n=1288	p-value
Primary renal disease			<0.0001
Diabetic nephropathy	48 [5.9]	134 [10.4]	
Glomerulonephritis	232 [28.7]	320 [24.9]	
Polycystic kidney disease	112 [13.9]	219 [17.0]	
Pyelonephritis	128 [15.8]	138 [10.7]	
Hypertensive nephropathy	37 [4.6]	89 [6.9]	
Renal vascular disease	9 [1.1]	29 [2.3]	
Other	157 [19.4]	194 [15.1]	
Uncertain	85 [10.5]	163 [12.7]	
Modified CCI			<0.0001
0	627 [77.6]	880 [68.5]	
1	91 [11.3]	170 [13.2]	
2	61 [7.6]	142 [11.1]	
≥3	29 [3.6]	92 [7.2]	
BMI			0.121
Underweight	23 [3.0]	26 [2.1]	
Normal	312 [40.8]	461 [37.5]	
Overweight	282 [36.9]	462 [37.6]	
Obese	147 [19.2]	281 [22.9]	
Smoking status			0.702
Non-smoker	437 [60.1]	710 [60.6]	
Smoker	78 [10.7]	137 [11.7]	
Ex-smoker	212 [29.2]	325 [27.7]	
Previous transplant	117 [14.5]	165 [12.9]	0.297
Highly sensitised (cRF>85%)	95 [11.7]	126 [9.8]	0.163
Pre-transplant treatment modality			<0.0001
Haemodialysis	352 [43.6]	737 [57.5]	
Haemodiafiltration	14 [1.7]	40 [3.1]	
Continuous ambulatory peritoneal dialysis	73 [9.1]	209 [16.3]	
Automated peritoneal dialysis	66 [8.2]	132 [10.3]	
Failing transplant	14 [1.7]	8 [0.6]	
Pre-emptive	288 [35.7]	156 [12.2]	

Data are median [IQR] or number [%]. Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Table 4.2.
p-value for chi-squared test.

There were also substantial geographic differences in the type of kidney transplants that were performed. The proportion of kidney transplants that were LDKTs was significantly higher in Northern Ireland at 68.9%, compared with 38.4% in England, 35.4% in Wales and 30.2% in Scotland (p<0.0001) for patients included in this study (Figure 4.4.).

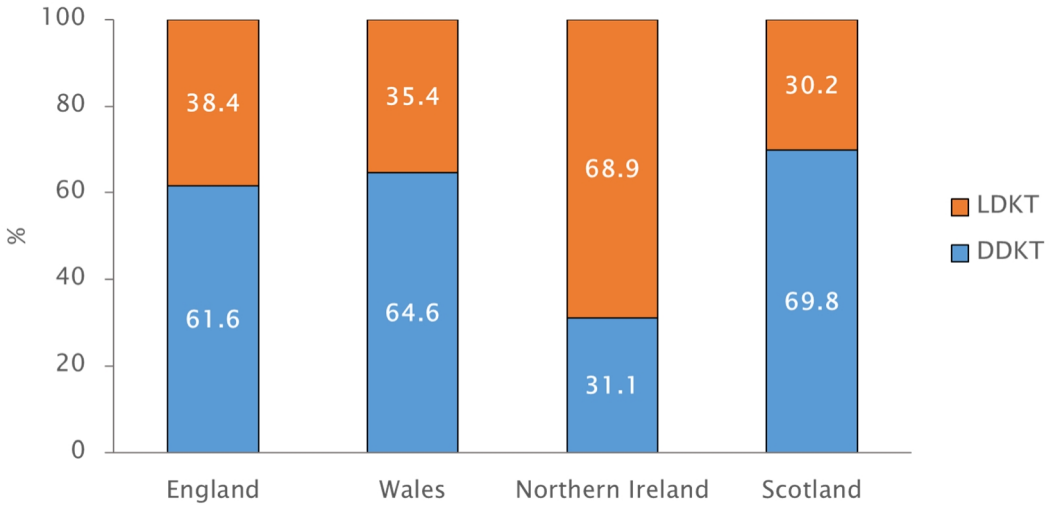

Figure 4.4. Distribution of type of transplants undertaken in each of the four UK countries

Donor characteristics are shown in Table 4.6. Compared to deceased donors, living donors were significantly younger and more likely to be female than deceased donors. A higher proportion of deceased donors were of White ethnicity compared with living donors. In all, 353 (43.9%) living donors were not genetically related to the recipient.

Table 4.6. Donor characteristics			
	Living donors n=812	**Deceased donors n=1288**	**p-value**
Median age (years)	48 [39 – 57]	54 [42 – 64]	<0.0001
Age group			<0.0001
0 – 17	0 [0]	31 [2.4]	
18 – 34	143 [17.6]	160 [12.4]	
35 – 49	298 [36.7]	303 [23.5]	
50 – 64	308 [37.9]	512 [39.8]	
65 – 75	61 [7.5]	234 [18.2]	
>75	2 [0.3]	48 [3.7]	
Gender			0.001
Male	379 [46.7]	696 [54.0]	
Female	432 [53.3]	592 [46.0]	
Ethnicity			<0.0001
White	720 [88.7]	1208 [95.2]	
Asian	52 [6.4]	21 [1.7]	
Black	28 [3.5]	23 [1.8]	
Other	12 [1.5]	17 [1.3]	
Donor-recipient relationship			-
Parent	147 [18.3]		
Son / Daughter	75 [9.3]		
Sibling	195 [24.3]		
Other blood relative	34 [4.2]		
Spouse / partner	188 [23.4]		
Pooled / altruistic	93 [11.6]		
Other non-related	72 [9.0]	1288 [100]	

Data are median [IQR] or number [%]. Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Table 4.2.
Wilcoxon test for median age. All others chi-squared test.

4.3.2. Factors associated with living donor kidney transplantation

Associations between recipient variables and the likelihood of undergoing LDKT versus DDKT were characterised using univariable and multivariable logistic regression (Tables 4.7, 4.8, 4.9).

Table 4.7. Univariable logistic regression analysis of recipient sociodemographic factors associated with LDKT versus DDKT

	Odds ratio [95% CI]	p-value
Recipient age group		
18 – 34	1 [ref]	
35 – 49	0.41 [0.32, 0.54]	<0.0001
50 – 64	0.27 [0.21, 0.35]	<0.0001
65 – 75	0.16 [0.11 ,0.23]	<0.0001
Recipient gender		
Male	1 [ref]	
Female	1.11 [0.92, 1.33]	0.268
Recipient ethnicity		
White	1 [ref]	
Asian	0.64 [0.47, 0.88]	0.006
Black	0.53 [0.35, 0.79]	0.002
Other	0.46 [0.21, 1.03]	0.060
Recipient civil status		
Married / Living with partner	1 [ref]	
Divorced / Separated / Widowed	0.47 [0.35, 0.63]	<0.0001
Single	1.09 [0.88, 1.35]	0.443
Recipient qualifications		
Higher education level	1 [ref]	
Secondary education level	0.73 [0.59, 0.92]	0.007
No qualifications	0.39 [0.29, 0.52]	<0.0001
Recipient employment status		
Employed	1 [ref]	
Unemployed	0.71 [0.50, 1.01]	0.059
Long term sick / disability	0.59 [0.47, 0.74]	<0.0001
Retired	0.44 [0.34, 0.57]	<0.0001
Other	1.18 [0.83, 1.68]	0.370
Recipient car ownership		
Yes	1 [ref]	
No	0.41 [0.31, 0.54]	<0.0001
Recipient home ownership		
Yes	1 [ref]	
No	0.86 [0.71, 1.04]	0.108
Recipient health literacy		
Normal	1 [ref]	
Limited	0.53 [0.39, 0.73]	<0.0001
Recipient english is first language		
Yes	1 [ref]	
No	0.61 [0.45, 0.82]	0.001
Recipient born in UK		
Yes	1 [ref]	
No	0.56 [0.43, 0.72]	<0.0001

CI; confidence interval, ref; reference

Table 4.8. Univariable logistic regression analysis of clinical and geographic factors associated with LDKT versus DDKT

	Odds ratio [95% CI]	p-value
Clinical variables		
Primary renal disease		
Diabetic nephropathy	1 [ref]	
Glomerulonephritis	2.02 [1.40, 2.93]	0.0002
Polycystic kidney disease	1.43 [0.96, 2.13]	0.082
Pyelonephritis	2.59 [1.72, 3.89]	<0.0001
Hypertensive nephropathy	1.16 [0.70, 1.92]	0.564
Renal vascular disease	0.87 [0.38, 1.96]	0.731
Other	2.26 [1.53, 3.34]	<0.0001
Uncertain	1.46 [0.86, 2.22]	0.081
Recipient modified CCI		
0	1 [ref]	
1	0.75 [0.57, 0.99]	0.041
2	0.60 [0.44, 0.83]	0.002
≥3	0.44 [0.29, 0.68]	0.0002
Recipient BMI (kg/m^2)		
Normal	1 [ref]	
Underweight	1.31 [0.73, 2.33]	0.365
Overweight	0.90 [0.73, 1.11]	0.327
Obese	0.77 [0.60, 0.99]	0.040
Recipient smoking status		
Non-smoker	1 [ref]	
Smoker	0.93 [0.68, 1.25]	0.614
Ex-smoker	1.06 [0.86, 1.31]	0.588
Recipient previous transplant		
No	1 [ref]	
Yes	1.15 [0.89, 1.48]	0.298
Recipient highly sensitised (cRF>85%)		
No	1 [ref]	
Yes	1.22 [0.92, 1.62]	0.164
Geographic variables		
Country		
England	1 [ref]	
Wales	0.88 [0.57, 1.35]	0.554
Northern Ireland	3.55 [2.15, 5.87]	<0.0001
Scotland	0.69 [0.50, 0.97]	0.030

CI; confidence interval, ref; reference

The multivariable model (Table 4.9) demonstrated that with each sequential increase in age group, there was a marked reduction in the probability of LDKT versus DDKT, such that patients aged 65-75 years had 89% lower odds of undergoing LDKT compared with patients aged 18-34 years (odds ratio [OR] 0.11, 95% confidence interval [CI] 0.07, 0.17, p<0.0001). Compared with White patients, Asian patients (OR 0.52, 95% CI 0.36, 0.74, p=0.0004) and Black patients (OR 0.60, 95% CI 0.38, 0.95, p=0.030) were less likely to undergo LDKT than DDKT. Having English as a first language and being born in the UK were significantly associated with LDKT on univariable analysis, however were not found to be significant in the multivariable model. This was due to very strong correlation between these variables and ethnicity (Ethnicity + English first language; Cramer's V=0.618, Ethnicity + Born in UK; Cramer's V=0.651, English first language + Born in UK; Cramer's V=0.740). Of the 3 variables, ethnicity showed the strongest association to LDKT and was retained in the final multivariable model. Patients who were divorced, separated or widowed (OR 0.62, 95% CI 0.45-0.86, p=0.004) and single (OR 0.75, 95% CI 0.56, 1.00, p=0.048) had a lower probability of LDKT compared with patients who were married or living with a partner. Having no formal qualifications (OR 0.55, 95% CI 0.40, 0.76, p=0.0002) and having only secondary education qualifications (OR 0.78, 95% CI 0.61, 1.00, p=0.049) reduced the odds of LDKT compared with patients with higher education qualifications. Health literacy was univariably associated with LDKT but was not significant in the multivariable model, due to its strong correlation with the qualification variable (Cramer's V=0.269). Not owning a car (OR 0.51, 95% CI 0.37, 0.71, p<0.0001) and not owning a home (OR 0.69, 95% CI 0.54, 0.89, p=0.0004) also decreased the odds of LDKT versus DDKT. With adjustment

for recipient variables, the odds of LDKT versus DDKT were over 3-fold higher for patients in Northern Ireland (OR 3.29, 95% CI 1.92, 1.42, p<0.0001) compared with patients in England. Further analysis by changing the reference value in the model showed the odds of LDKT in Northern Ireland were also higher than in Wales (OR 3.62, 95% CI 1.80, 7.30, p=0.0003) and Scotland (OR 4.43, 95% CI 2.36, 8.31, p<0.0001). There were no significant differences in the likelihood of undergoing LDKT in England, Wales and Scotland.

Table 4.9. Multivariable logistic regression analysis of factors associated with LDKT versus DDKT

	Odds ratio [95% CI]	p-value
Recipient age group		
18 – 34	1 [ref]	
35 – 49	0.34 [0.25, 0.47]	<0.0001
50 – 64	0.19 [0.14, 0.27]	<0.0001
65 – 75	0.11 [0.07, 0.17]	<0.0001
Recipient ethnicity		
White	1 [ref]	
Asian	0.52 [0.36, 0.74]	0.0004
Black	0.60 [0.38, 0.95]	0.030
Other	0.46 [0.19, 1.09]	0.079
Recipient civil status		
Married / Living with partner	1 [ref]	
Divorced / Separated / Widowed	0.62 [0.45, 0.86]	0.004
Single	0.75 [0.56, 1.00]	0.048
Recipient qualifications		
Higher education level	1 [ref]	
Secondary education level	0.78 [0.61, 1.00]	0.049
No qualifications	0.55 [0.40, 0.76]	0.0002
Recipient car ownership		
Yes	1 [ref]	
No	0.51 [0.37, 0.71]	<0.0001
Recipient home ownership		
Yes	1 [ref]	
No	0.69 [0.54, 0.89]	0.004
Country		
England	1 [ref]	
Wales	0.88 [0.55, 1.42]	0.603
Northern Ireland	3.29 [1.92, 5.63]	<0.0001
Scotland	0.72 [0.50, 1.04]	0.082

CI; confidence interval, ref; reference

4.3.3. Factors associated with living donor kidney transplantation amongst kidney transplant recipients of White ethnicity

A sensitivity analysis was conducted in a subgroup of White patients only using the same modelling methods as above. This confirmed that the effects

of socioeconomic factors on the likelihood of LDKT versus DDKT were independent of ethnicity (Table 4.10).

Table 4.10. Multivariable logistic regression analysis of factors associated with LDKT versus DDKT in a subgroup of White patients

	Odds ratio [95% CI]	p-value
Recipient age group		
18 – 34	1 [ref]	
35 – 49	0.31 [0.22, 0.44]	<0.0001
50 – 64	0.17 [0.11, 0.24]	<0.0001
65 – 75	0.10 [0.06, 0.16]	<0.0001
Recipient civil status		
Married / Living with partner	1 [ref]	
Divorced / Separated / Widowed	0.59 [0.42, 0.83]	0.003
Single	0.68 [0.49, 0.94]	0.018
Recipient qualifications		
Higher education level	1 [ref]	
Secondary education level	0.75 [0.57, 0.98]	0.035
No qualifications	0.53 [0.37, 0.75]	0.0004
Recipient car ownership		
Yes	1 [ref]	
No	0.51 [0.36, 0.75]	0.0004
Recipient home ownership		
Yes	1 [ref]	
No	0.71 [0.54, 0.95]	0.019
Country		
England	1 [ref]	
Wales	0.93 [0.57, 1.52]	0.774
Northern Ireland	3.47 [2.00, 6.01]	<0.0001
Scotland	0.73 [0.50, 1.06]	0.101

CI; confidence interval, ref; reference

4.3.4. Factors associated with pre-emptive living donor kidney transplantation

A further subgroup analysis in the LDKT group examined factors associated with achieving pre-emptive transplantation versus transplantation after the initiation of dialysis (Table 4.11). Patients with a previous transplant were

excluded, because pre-emptive transplantation refers to the receipt of a kidney transplant before the point at which maintenance dialysis is required due to a progressive deterioration in renal function, and is therefore only relevant to patients undergoing their first transplant. Multivariable modelling demonstrated a significantly decreased likelihood of pre-emptive LDKT for Asian patients (OR 0.45, 95% CI 0.24, 0.87, p=0.017), unemployed patients (OR 0.46, 95% CI 0.22, 0.97, p=0.042), patients unable to work due to long term sickness/disability (OR 0.46, 95% CI 0.30, 0.72, p=0.0006), retired patients (OR 0.47, 95% CI 0.29, 0.75, p=0.002), not owning a car (OR 0.35, 95% CI 0.16, 0.74, p=0.006) and not owning a home (OR 0.64, 95% CI 0.43, 0.95, p=0.027).

Table 4.11. Multivariable logistic regression analysis of factors associated with pre-emptive LDKT

	Odds ratio [95% CI]	p-value
Recipient ethnicity		
White	1 [ref]	
Asian	0.45 [0.24, 0.87]	0.017
Black	1.24 [0.56, 2.75]	0.604
Other	1.14 [0.17, 7.54]	0.895
Recipient employment status		
Employed	1 [ref]	
Unemployed	0.46 [0.22, 0.97]	0.042
Long term sick / disability	0.46 [0.30, 0.72]	0.0006
Retired	0.47 [0.29, 0.75]	0.002
Other	1.38 [0.78, 2.45]	0.271
Recipient car ownership		
Yes	1 [ref]	
No	0.35 [0.16, 0.74]	0.006
Recipient home ownership		
Yes	1 [ref]	
No	0.64 [0.43, 0.95]	0.027

CI; confidence interval, ref; reference

4.4. Discussion

Amongst patients undergoing kidney transplantation in the UK, there are significant age, ethnic, socioeconomic and geographic disparities in the utilisation of living donor versus deceased donor kidney transplantation. Older age, Black and Asian ethnicity, being divorced, separated, widowed or single, lower educational attainment and measures of greater socioeconomic deprivation (non car and home ownership) were significantly and independently associated with a reduced likelihood of LDKT versus DDKT. For the period of the study, geographic differences were also noted, with patients in Northern Ireland having a greater probability of LDKT versus DDKT compared with patients in the rest of the UK. Furthermore, the study demonstrated that amongst those who do undergo LDKT, ethnic and socioeconomic disparities persist in determining whether LDKT is received pre-emptively.

In recent years, a great deal of attention has been directed towards addressing disparities in access to DDKT in the UK. Individuals who are older, more socially deprived, from ethnic minority backgrounds or treated in certain transplant centres are less likely to be put on the waiting list for and subsequently receive DDKT.[3-5, 117, 130] Despite LDKT providing optimal clinical outcomes for patients with ESRD, there have been limited data on whether patients experience disparities in utilising this treatment. Udayaraj et al. reported a lower probability of LDKT for patients with greater socioeconomic deprivation and patients from Black and South Asian backgrounds in the UK.[118] However, Udayaraj examined the rates of LDKT amongst patients

starting RRT, without adjustment for comorbidity. Therefore, a major confounding factor in their study is the higher rate of comorbidity amongst more socioeconomically deprived and ethnic minority populations, which provides an alternative explanation for their reduced likelihood of LDKT due to medical unsuitability for transplantation. In our study we avoided the confounding effect from comorbidity by collecting extensive comorbidity data and also by choosing to examine a cohort of patients who were all deemed suitable to undergo transplantation. This is a select population of patients who have already successfully navigated the process of transplant referral, evaluation and listing. Therefore, it is concerning that the striking disparities observed appear to occur over and above the well-recognised inequities that patients face before even reaching this stage. These findings are not confined to the UK. Our results are consistent with those of a US study by Gore et al. which reported lower odds of LDKT relative to DDKT for patients who were older, from ethnic minority groups, with lower socioeconomic status and lower levels of education.[131] Roodnat et al. showed the same factors reduced the likelihood of LDKT versus DDKT in the Netherlands.[132] It is interesting that similar results have been demonstrated both within publicly funded as well as private healthcare systems, suggesting factors other than financial disadvantage play an important role.

The well-recognised markers of socioeconomic deprivation (car ownership and home ownership) were strongly associated with a reduced likelihood of LDKT versus DDKT in this study. A subgroup analysis of White patients only confirmed that the effects of socioeconomic deprivation were independent of ethnicity. Lower rates of LDKT in socioeconomically deprived patients have

also been reported in Australia[133] and the US[134, 135]. The reasons behind this finding are unclear. It is known that living donor-recipient pairs usually come from the same socioeconomic group.[136] Greater socioeconomic deprivation is linked to poorer health,[137] potentially limiting the pool of living donors available to more deprived patients. In the UK, kidney transplantation including medication and after-care are provided free of charge under the National Health Service (NHS). However, it is possible that other costs such as transportation, childcare and lost income from time off work could play a role in deterring potential living donors or deterring those in need of a kidney from approaching potential donors.[138] A financial reimbursement policy for expenses incurred by living donors does exist in the UK, but it may not be implemented consistently by transplant centres. A recent qualitative study of DDKT recipients found that many were unaware of the living donor reimbursement policy.[48] Despite this, socioeconomically deprived patients have been reported as not perceiving financial concerns to be a major barrier to LDKT in the UK, whereas passivity and disempowerment in treatment decisions, short-term focus and lack of social support were seen as more significant obstacles to LDKT.[48]

It is well recognised that ethnic minority patients wait longer for DDKT in the UK, due to the mismatch between the HLA types of minority patients and those of the predominantly White donor pool.[78] One might therefore expect a higher uptake of LDKT in ethnic minority patients. Our study found the opposite, with patients from Black and Asian backgrounds having lower odds of LDKT than DDKT, compared with White patients. The effect of ethnicity on the likelihood of LDKT was independent to the effects of social deprivation

and education. Similar disparities have been reported in the US[129, 139] and Canada.[140] These disparities have worsened over time, and are likely contributing to differences in outcomes between White and non-White patients.[141, 142] One US study showed that while the rates of LDKT have increased amongst White patients between 1995 and 2014, they have decreased for Blacks and Hispanics over the same time period.[142] Possible explanations cited for these disparities include cultural and religious beliefs,[143, 144] reluctance to engage with the medical system,[145, 146] institutional prejudice[147, 148] and language barriers.[149] In our analysis, having English as a first language was univariably associated with LDKT, and was highly correlated to ethnicity. However, English as a first language was not significant in the multivariable model, and it did not attenuate the effect of the Ethnicity variable. Thus the language barrier does not appear to explain the lower access to LDKT by ethnic minorities. Being born outside of the UK was also associated with a lower likelihood of LDKT on univariable analysis and was highly correlated to ethnicity but not significant on multivariable analysis. However, adding this variable to the multivariable model did reduce the association of the ethnicity variable with LDKT, specifically for Black patients. Thus, being born outside of the UK partially accounts for some of the association of Black ethnicity with reduced access to LDKT. One potential explanation for this is that a high proportion of the potential donors available to Black patients who are born outside of the UK (e.g. family members) may reside in other countries. There is currently a policy in place in the UK that allows non-UK residents to be considered as potential donors.[150] The process is logistically complex and involves arranging blood tests to be sent to the UK for matching, organising investigations and medical review in the donors

country and application to the home office for a visa to allow the donor to enter the UK, supported by a letter from the recipient's transplant centre. The recipient must provide evidence that they will be able to provide accommodation for the donor during their stay in the UK, and there is a process for claiming reimbursement of travel expenses. There is no data available on whether patients are aware of this policy, how often the policy is utilised and how often visa applications are rejected. However, increasing public awareness of the policy and identifying parts of the process which could be improved, may help to increase access to LDKT for some ethnic minority recipients. Another potential reason for the lower rates of LDKT in ethnic minority patients is concern over a higher risk for living donors from minority ethnic backgrounds.[22, 151, 152] It is known that ethnic minorities have a higher prevalence of hypertension and diabetes with associated ESRD, and thus patients from these backgrounds are more likely to be excluded from kidney donation.[153, 154] As such, ethnic minority patients may have to consider a much wider range of potential donors before being able to identify a medically suitable and willing donor, and efforts should be made to aid patients in this process.

We have demonstrated that a patient's level of educational attainment is independently associated with their likelihood of LDKT versus DDKT. Higher educational attainment may be linked to a better ability to understand the benefits of LDKT and participate in informed and shared decision making. Education is an important modifiable determinant of LDKT disparities. We found that educational attainment was highly correlated with health literacy. Health literacy is an individuals' capacity to obtain, process and understand

health information and services needed to make appropriate health decisions.[155] Health literacy has been shown to be an important factor for both potential kidney transplant recipients as well as potential living donors in successfully navigating the living donation and transplantation process.[156] Although both educational attainment and health literacy were significantly associated with LDKT on univariable analysis in our study, educational attainment was the stronger risk factor and thus was retained in the final multivariable model. This suggests that more advanced academic achievement confers an additional advantage above and beyond having "normal" health literacy. This could relate to other aspects of the LDKT journey and may reflect further targets for interventions. For example, the ability to communicate with and convey information to potential donors may be equally important as the ability to understand information about LDKT. As the health literacy variable was self-reported, another potential explanation is that there is a discrepancy between patients' own perception of their level of health literacy and their actual level of health literacy. This would be supported by the fact that 25.7% of DDKT recipients were recorded as having no qualifications, whereas only 13.5% reported limited health literacy.

The finding that patients who were married or living with a partner had better access to LDKT is likely to be related to the opportunity for spousal donation. Spouses represented a considerable proportion (23.4%) of living donors in this study. Being married or living with a partner may also confer other benefits such as having a better social support network or access to more unrelated or son/daughter donors.

Older age was associated with dramatically reduced odds of LDKT versus DDKT. Previous research has demonstrated that older age is associated with a lower probability of attempted donor recruitment.[157] Older patients have reported an unwillingness to put younger donors at risk, particularly their children.[158] In our study 18.3% of the living donors were parents whereas only 9.3% were sons/daughters.

Despite adjustment for demographic and socioeconomic factors, we found striking geographic differences in LDKT activity, with patients in Northern Ireland experiencing significantly higher odds of LDKT versus DDKT compared with patients in England, Wales and Scotland. Our results reflect the actual number of LDKTs pmp which were around twice as high in Northern Ireland (31.1 pmp) compared with the rest of the UK (England 15.9 pmp, Wales 16.6 pmp, Scotland 10.9 pmp) at the time of the study.[159] Around this time, an initiative was instigated in Northern Ireland to promote LDKT and pre-emptive transplantation as the treatment of choice. The key measures included education to promote a change of mind-set amongst nephrologists (particularly non-transplant nephrologists) as well as the entire transplant team, together with improved infrastructure and more streamlined services to enable timely work-up and transplantation (e.g. one-stop living donor assessment clinic). Effective leadership, persistence and gaining the support of commissioners and management were critical in achieving these changes (personal communication, A. Courtney, 17/01/2017). Our results and the national figures indicate that such a strategy can be very successful in increasing LDKT utilisation. The higher LDKT rate in Northern Ireland has resulted in a substantial reduction in the DDKT waiting list. In 2018, the

number of patients on the active kidney transplant waiting list in Northern Ireland was 50 pmp, compared with 77.8 pmp in England, 60.8 in Wales and 79.6 in Scotland.[14] Moreover, the number of LDKTs in Northern Ireland has continued to increase (35.5 pmp in 2018, one of the highest in the world), demonstrating that the changes have led to a sustained improvement rather than a temporary peak in activity. This is encouraging when exploring potential avenues to improve LDKT across the UK as a whole.

Our study showed for the first time in the UK that socioeconomic deprivation, unemployment and Asian ethnicity were independently associated with a lower likelihood of pre-emptive LDKT. These findings are consistent with studies from the US and Australia.[20, 131, 133] The disparity experienced by socioeconomically deprived individuals is likely to be related to an increased likelihood of late referral to specialist renal services,[160] however this does not explain the disparity for patients of Asian ethnicity.

A major strength of the present study is that we recruited all patients prospectively and collected accurate, reliable and comprehensive data. A large proportion (73%) of the national adult kidney transplant population were included in the study. Nevertheless, as it was not possible to recruit the entire kidney transplant population, it must be recognised that the study is limited by a risk of selection bias. Reassuringly, the age, gender and ethnicity distribution of study participants were not significantly different to the national adult kidney transplant population. Furthermore, the study cohort included patients from all 23 UK renal transplant centres as well as nationally comparable proportions of LDKT, DDKT and pre-emptive recipients, thereby

reducing the potential for bias. However, differences in other unmeasured characteristics between study participants and non-participants cannot be ruled out. Furthermore, due to the observational nature of the study, the results can only describe associations, and as such causality of the observed relationships cannot be inferred.

LDKT, and in particular pre-emptive LDKT provides optimal clinical outcomes for patients with ESRD, yet its uptake is variable within the UK. This study has identified specific patient groups with a lower likelihood of undergoing LDKT relative to DDKT. We have demonstrated that demographic, socioeconomic and geographic factors are more strongly associated with the type of transplant received, than clinical factors including comorbidity, primary renal disease, BMI, HLA sensitisation or previous transplantation. It is concerning that even amongst patients who do attain LDKT, additional disparities affect the chance of receiving pre-emptive transplantation. This demonstrates the strength of social factors in influencing access to healthcare and may reflect similar inequities across a wide range of healthcare services. The demonstrated disparities may reflect both barriers in certain patient groups as well as important positive factors in others. Furthermore, these influencing factors are likely to apply to both potential recipients and donors. Equity is a core value of the NHS, therefore if particular patient groups experience avoidable barriers to receiving a LDKT or donating a kidney, there is a responsibility to provide tailored resources to remove these barriers. Improving access to LDKT will not only benefit individual patients, but will also have favourable effects for the wider ESRD population by effectively increasing the overall pool of available organs and thus reducing the size of

the transplant waiting list. However, both donor and recipient welfare and autonomy undoubtedly remain the primary focus. Some patients may prefer not to pursue LDKT due to concerns about risks to their potential donors, just as some potential donors may decide against donation.[158, 161] The aim is not to persuade all patients to undergo LDKT but to provide all patients with equitable opportunity to explore the option of LDKT. Identifying disadvantaged patient groups is an essential first step towards improving equity in access to LDKT. The findings of this study can guide further research into the development of targeted interventions. Several studies in the US have explored strategies including culturally sensitive education programs,[162, 163] home-based education[164, 165] and patient advocates[166] with promising results for reducing disparities in LDKT. Recently, some initiatives in the UK have also been launched. The "Acceptance, Choice and Empowerment in Living Donor Kidney Transplantation" (ACE LDKT) is a pilot study funded by NHSBT, and uses volunteers as peer educators in a home-education programme for Black and Asian patients with ESRD.[167] Two pilot sites are enrolled; West Midlands (Queen Elizabeth Hospital, Birmingham Asian patients) and South London (Guy's & St. Thomas' Foundation Trust, London, African and Caribbean patients). Home education is also currently being explored in Edinburgh where tailored education about LDKT and other treatment options is delivered by a dedicated home educator (Renal Education and choices at home - REACH project). The results of these studies are eagerly awaited, and other similar programs should be pursued in order to improve equity of access to LDKT across the whole of the UK.

CHAPTER 5

Impact of Recipient Comorbidity on Graft and Patient Survival after Kidney Transplantation

5.1. Introduction

The demographics of the kidney transplant population have changed considerably in recent years. For example, over the past decade, the proportion of deceased donor kidney transplant recipients older than 60 years of age has increased from 15% to 32% in the UK (Figure 5.1).[13] Accordingly, the burden of comorbidity among patients undergoing kidney transplantation has grown substantially.[62, 168, 169] Comorbidities such as diabetes, hypertension and obesity which contribute to the development of end stage renal disease (ESRD) are on the rise,[170] while ESRD itself is an important risk factor for conditions such as cardiovascular disease.[171, 172]

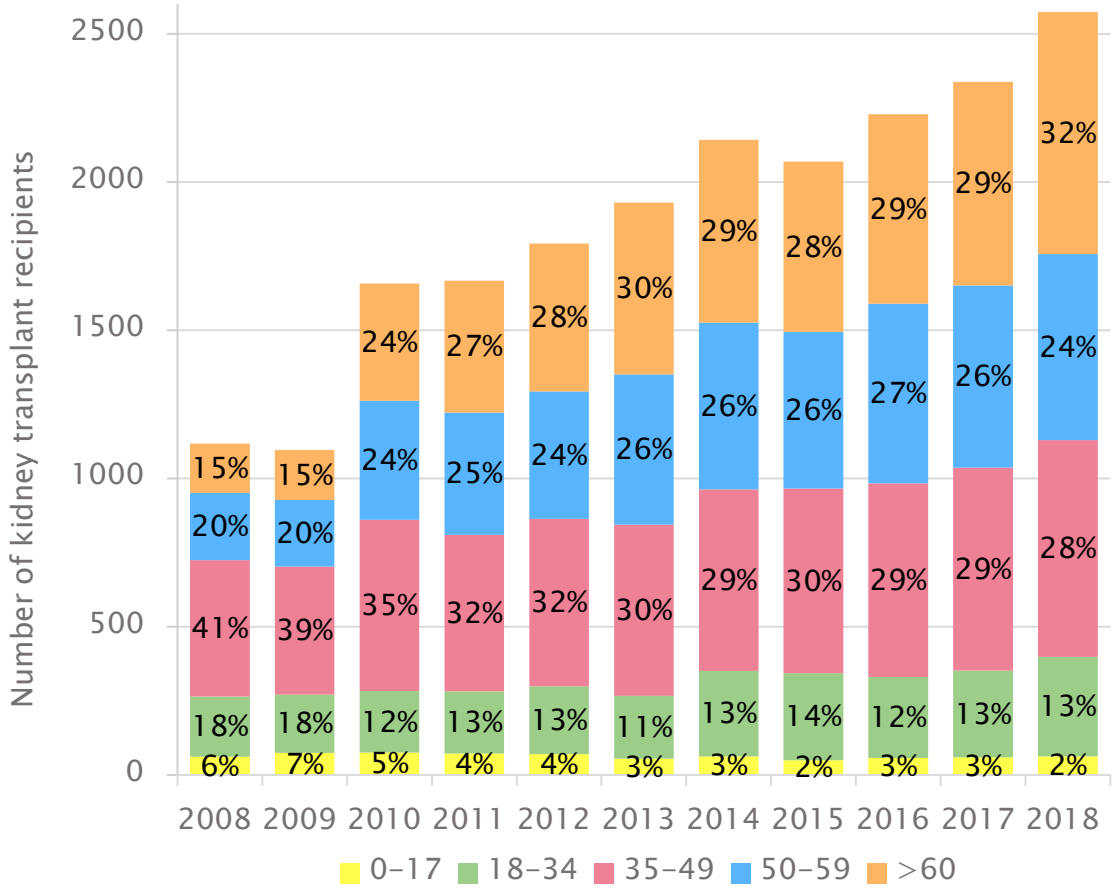

Figure 5.1. Deceased donor kidney transplant recipients by age group (Source: NHS Blood and Transplant annual activity reports 2008–2018)[13]

With continued advances in transplant care, the influence of more traditionally reported immunological and transplant related factors on post-transplant outcomes is diminishing, and patient factors such as comorbidity likely play an increasingly important role in both graft and patient survival.[173-177]

Despite this, there is a lack of evidence for how recipient comorbidity may affect transplant outcomes. A small number of studies have demonstrated the overall detrimental effect of comorbidity on transplant outcomes using various comorbidity indices.[62, 94, 178, 179] However, this does not allow characterisation of the risks associated with specific comorbid conditions and as such is of limited value when assessing individual patient risks. Retrospective registry analyses have identified some comorbidities as risk factors for transplant outcomes, but the results show considerable heterogeneity and are limited by the reliability of registry data.[180-182] Furthermore, many studies investigating factors that affect transplant outcomes use a composite outcome that combines graft failure and patient death.[169, 183] This is often seen as a useful outcome as it demonstrates the "overall" success of the transplant. However, the risk factors that increase the risk of graft loss are likely to be different to those for patient death, and more in depth analysis is required to distinguish and characterise specific risks.

Understanding how different comorbid conditions affect both graft and patient survival is essential for assessing the suitability of patients for transplantation, for fully informed discussion with patients regarding their individual risks and outcomes and for facilitation of shared decision making

and informed consent. The aim of this analysis was to investigate the impact of recipient baseline comorbidity on two year survival outcomes following kidney transplantation, in a national prospective cohort study.

5.2. Methods

5.2.1. Study population

The study population for this analysis was the incident transplant cohort of ATTOM. This consists of 2262 kidney transplant recipients recruited at the time of transplantation, from all 23 UK transplant centres. Full details of the recruitment methods are included in Chapter 2. For the purposes of this analysis, patients undergoing multi-organ transplants other than simultaneous pancreas-kidney (SPK) transplants were excluded (n=12). The cohort included kidney only (KO) (n=2100) and SPK (n=150) transplant recipients. Both deceased donor (n=1438) and living donor (n=812) transplants were included.

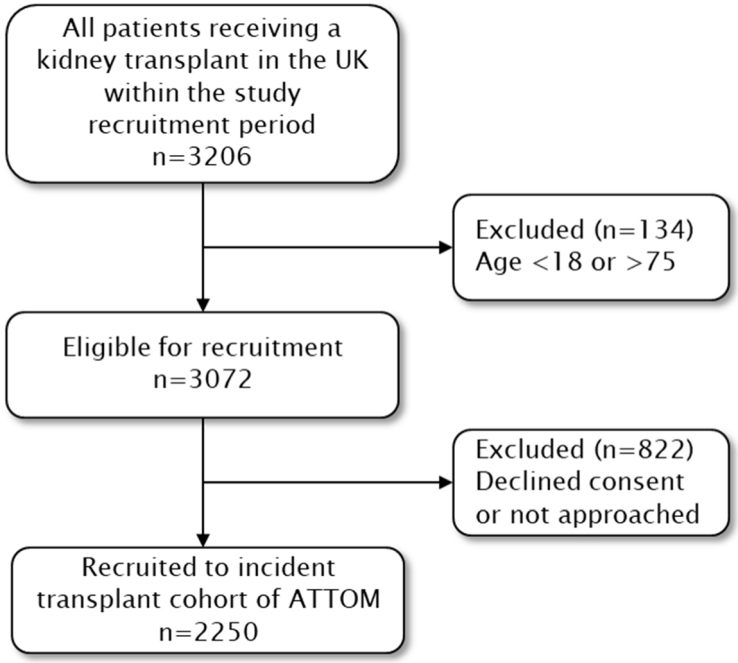

Figure 5.2. Study population

Thus, the final study population included 2250 kidney transplant recipients. The cohort represented 73.2% of the national kidney transplant population who were eligible for recruitment to the study (Figure 5.2).

5.2.2. Study design and data variables

This was a prospective cohort study. Baseline recipient comorbidity data as well as a number of other recipient, donor and transplant variables were collected at the time of transplantation (Appendix A.2.). Patients were then followed up for two years from the date of transplant. The relationship between baseline comorbidity and two year survival outcomes were analysed, adjusting for relevant confounders.

The exposure variables of interest included diabetes, obesity (body mass index [BMI] ≥30), ischaemic heart disease, heart failure, atrial fibrillation, cardiac valve replacement, pacemaker, cerebrovascular disease (CVD), peripheral vascular disease (PVD), abdominal aortic aneurysm, chronic respiratory disease, chronic liver disease (CLD), blood borne viruses, malignancy, mental illness and dementia (definitions given in Appendix A.3.).

The primary outcome measures were graft survival, patient survival and transplant survival. Graft survival was defined as the time from transplantation to graft failure (graft failure defined as the earliest of return to dialysis or re-transplantation), with censoring for death with a functioning graft, at last follow-up or at 2 years. Patient survival was defined as the time from transplantation to patient death, with censoring at last follow-up or at 2 years. Transplant survival was defined as the time from transplantation to

the earliest of graft failure or patient death, with censoring at last follow-up or at 2 years.

Potential confounders considered in multivariable analyses included:

(a) recipient variables: age, gender, ethnicity, primary renal disease, time on dialysis, smoking status, previous transplantation, sensitisation level, blood group

(b) donor variables: age, gender, ethnicity, blood group, BMI

(c) transplant variables: human leukocyte antigen (HLA) mismatches (MM), type of transplant (living donor KO, deceased donor KO or SPK), cold ischaemic time (CIT)

Variable definitions are given in Appendix A.3. Recipient calculated reaction frequency (cRF) ≥85% was used to define highly sensitised recipients, in line with the NHS Blood and Transplant (NHSBT) definition.[79] BMI was grouped in accordance with the World Health Organisation (WHO) BMI classifications of Underweight (<18.5 kg/m^2), Normal (18.5 - 24.9 kg/m^2), Overweight (25.0 - 29.9 kg/m^2) and Obese (≥30.0 kg/m^2).[126] HLA mismatches were classified into 4 levels as defined by the current UK deceased donor kidney allocation scheme: level 1 (000 HLA-A, B, DR MM), level 2 (0DR + 0/1B MM), level 3 (0DR + 2B MM) or (1DR + 0/1B MM) and level 4 (1DR + 2B MM) or (2DR MM).[61] A donor risk index for UK deceased donor kidneys has previously been described by Watson et al,[184] however, the risk index was developed specifically for deceased donor kidneys. In the current analysis, both living and deceased donor kidney transplants were included because the focus was on the impact of recipient comorbidity rather than donor factors on

outcomes. Therefore, the UK kidney donor risk index was not suitable for use in this analysis, and models were adjusted for individual donor factors including donor type instead.

5.2.3. Statistical methods

Baseline characteristics were presented as numbers with percentages (%) and medians with interquartile ranges (IQR). Categorical data were compared by chi-squared test or Fisher's exact test. The impact of recipient comorbidity on 2 year graft, patient and transplant survival was examined using Kaplan-Meier survival curves and the log-rank test, as well as univariable and multivariable Cox proportional hazards regression. Multivariable models were constructed using a manual backward elimination method. All comorbidities were considered for inclusion in the multivariable models. Potential confounding variables with a p-value of <0.15 on univariable analysis were included in the initial model. The importance of each variable in the multivariable model was then tested by examining the difference in log-likelihood between the model with and without the variable. If the difference was not significant ($p>0.05$) on testing with a likelihood ratio test, the variable was removed. The effect of removing each of the remaining variables was retested until the most parsimonious model was achieved. A decision was made *a priori* to retain the type of transplant and recipient age variables in all models due to clinical relevance. Continuous variables were explored as linear, fractional polynomials and categorical variables. Potential interactions between variables were tested, none were significant. Correlation between categorical variables was tested using Cramer's V correlation coefficient, with values >0.15 considered to show strong correlation.[127] The proportional hazards

assumption was tested using log cumulative hazards plots and Schoenfeld residuals and found to be satisfied for all variables. A frailty model with transplant centre as a random effect was used to check for between-centre variation in survival. The extent of missing data did not exceed 10% for any one variable (Table 5.1). For modelling purposes, missing values of covariates were imputed using the fully conditional specification logistic regression method to produce ten imputed datasets (using the SAS procedure PROC MI). Outcome data were not imputed. Each imputed dataset was modelled separately and then estimates were combined (using the SAS procedure PROC MIANALYZE). Models using a dataset with deletion of missing values rather than imputed values were checked and did not change conclusions. All analyses were conducted using SAS® 9.4 (SAS Institute Inc, Cary, USA).

5.2.4. Sensitivity analyses

To test the robustness of the results, the analyses described above were also performed on three sub-cohorts:

(a) kidney only transplant recipients i.e. excluding the SPK recipients

(b) first transplant recipients i.e. excluding patients with a previous transplant

(c) deceased donor transplant recipients i.e. excluding living donor transplant recipients

Table 5.1. Missing data	
Variable	n [%]
Diabetes	6 [0.3]
Ischaemic heart disease	10 [0.4]
Heart failure	9 [0.4]
Atrial fibrillation	9 [0.4]
Cardiac valve replacement	12 [0.5]
Pacemaker	10 [0.4]
Cerebrovascular disease	10 [0.4]
Peripheral vascular disease	10 [0.4]
Abdominal aortic aneurysm	10 [0.4]
Chronic respiratory disease	9 [0.4]
Chronic liver disease	9 [0.4]
Blood borne viruses	10 [0.4]
Malignancy	9 [0.4]
Mental illness	9 [0.4]
Dementia	11 [0.5]
Recipient BMI	123 [5.5]
Recipient age	0 [0]
Recipient gender	0 [0]
Recipient ethnicity	9 [0.4]
Primary renal disease	11 [0.5]
Time on dialysis	0 [0]
Smoking status	215 [9.6]
Previous transplantation	12 [0.5]
Sensitisation level	0 [0]
Recipient blood group	0 [0]
Donor age	0 [0]
Donor gender	1 [0.04]
Donor ethnicity	23 [1.0]
Donor blood group	0 [0]
Donor BMI	93 [4.1]
HLA MM level	0 [0]
Transplant type	0 [0]
CIT	87 [3.9]
Graft survival	5 [0.2]
Patient survival	4 [0.2]
Transplant survival	5 [0.2]

5.3. Results

5.3.1. Study population characteristics

The study population represented 73.2% of all patients undergoing kidney transplantation during the study recruitment period who were eligible for recruitment to the study (Figure 5.2.). Patient demographics of the national adult kidney transplant population (n=3072) were compared to the study population (n=2250) using the one sample chi-square goodness of fit test (Table 5.2). Compared with the national kidney transplant population, the recruited study population had a similar distribution of age, gender and type of transplant, but comprised of a significantly higher proportion of White patients and fewer patients from Black, Asian and other ethnic backgrounds.

Table 5.2. Demographics of kidney transplant recipients – national population versus study population

Variable	National kidney transplant population (%)	ATTOM kidney transplant population (%)	p-value
Age group			0.982
18 – 34	17.3	17.5	
35 – 49	31.8	31.6	
50 – 64	36.8	37.0	
65 – 75	14.1	13.9	
Gender			0.769
Male	62.5	62.8	
Female	37.5	37.2	
Ethnicity			0.030
White	80.6	82.5	
Asian	10.5	9.3	
Black	6.5	6.2	
Other	1.5	1.6	
Missing	0.9	0.4	
Type of transplant			0.899
KO	93.4	93.3	
SPK	6.6	6.7	

Baseline recipient, donor and transplant characteristics for the entire study cohort (n=2250) are shown in Tables 5.3 and 5.4. Both recipients and donors had a median age of 50 years, were predominantly male and of White ethnicity. The primary renal disease was diabetes in 322 (14.8%) patients. Most patients underwent dialysis prior to transplantation, however 483 (21.5%) patients received a pre-emptive transplant. Overall, 2100 patients received a kidney-only transplant (812 living donor, 1288 deceased donor) and 150 patients received an SPK transplant.

Table 5.3. Baseline recipient characteristics of the study cohort		
Age, years	50	[40 – 60]
Gender		
Male	1413	[62.8]
Female	837	[37.2]
Ethnicity		
White	1857	[82.9]
Asian	209	[9.3]
Black	140	[6.3]
Other	35	[1.6]
Primary renal disease		
Polycystic kidney disease	332	[14.8]
Diabetic nephropathy	322	[14.4]
Glomerulonephritis	554	[24.7]
Pyelonephritis	266	[11.9]
Hypertensive nephropathy	126	[5.6]
Renal vascular disease	39	[1.7]
Other	351	[15.7]
Uncertain	249	[11.1]
Time on dialysis		
Pre-emptive	483	[21.5]
0 – 1 year	380	[16.9]
1 – 3 years	590	[26.2]
3 – 5 years	361	[16.0]
> 5 years	436	[19.4]
Smoking status		
Non-smoker	1206	[59.3]
Smoker	239	[11.7]
Ex-smoker	590	[29.0]
Previous transplant	292	[13.1]
Highly sensitised [cRF≥85%]	233	[10.4]
Recipient blood group		
A	909	[40.4]
B	267	[11.9]
AB	101	[4.5]
O	973	[43.2]

Data are median [IQR] or number [%].

Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Table 5.1.

Table 5.4. Baseline donor and transplant variables		
Donor variables		
Donor age, years	50	[40 – 60]
Donor gender		
Male	1148	[51.0]
Female	1101	[49.0]
Donor ethnicity		
White	2065	[92.7]
Asian	78	[3.5]
Black	52	[2.3]
Other	32	[1.4]
Donor BMI, kg/m^2		
Underweight [<18.5]	0	[0.0]
Normal [18.5 – 24.9]	809	[37.5]
Overweight [25.0 – 29.9]	929	[43.1]
Obese [≥30.0]	419	[19.4]
Donor blood group		
A	849	[37.7]
B	225	[10.0]
AB	64	[2.8]
O	1112	[49.4]
Transplant variables		
HLA MM level		
1	248	[11.0]
2	470	[20.9]
3	1090	[48.4]
4	442	[19.6]
Transplant type		
Living donor KO	812	[36.1]
Deceased donor KO	1288	[57.2]
SPK	150	[6.7]
CIT (hours)	11.3	[4.0 – 15.7]

Data are median [IQR] or number [%].
Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Table 5.1.

The prevalence of comorbidity at the time of transplantation among all recipients in the study is shown in Table 5.5. The most common comorbidity among kidney transplant recipients was obesity (20.6%), followed by diabetes (19.5%), ischaemic heart disease (8.6%) and chronic respiratory disease (7.8%).

At the time of transplantation, 44.2% patients had no comorbidity, 34.5% had 1 comorbidity, 14.4% had 2 comorbidities and 6.9% had 3 or more comorbidities.

Table 5.5. Prevalence of recipient comorbidity in the study cohort

	n	[%]
Diabetes	437	[19.5]
Ischaemic heart disease	193	[8.6]
Heart failure	55	[2.5]
Atrial fibrillation	37	[1.7]
Cardiac valve replacement	19	[0.9]
Pacemaker	15	[0.7]
Cerebrovascular disease	111	[5.0]
Peripheral vascular disease	74	[3.3]
Abdominal aortic aneurysm	6	[0.3]
Chronic respiratory disease	174	[7.8]
Chronic liver disease	40	[1.8]
Blood borne viruses	51	[2.3]
Malignancy	144	[6.4]
Mental illness	133	[5.9]
Dementia	2	[0.1]
BMI, kg/m^2		
Underweight (<18.5)	52	[2.4]
Normal (18.5 – 24.9)	851	[40.0]
Overweight (25.0 – 29.9)	786	[37.0]
Obese (≥30.0)	438	[20.6]

Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Table 5.1.

5.3.2. Impact of recipient comorbidity on 2 year graft survival

Of the 2250 kidney transplant recipients in the study, 5 patients had missing data for graft survival. Among the 2245 patients with complete graft survival data, 113 (5.0%) experienced graft failure within the 2 year follow up period, 69 (3.1%) were censored due to death with a functioning graft, 183 (8.2%) were censored at last follow-up and 1880 (83.7%) were censored at 2 years. Of the

183 patients censored at last follow up, median censoring time was 670 days (IQR 365 - 707 days). Of the 113 graft failures, 40 (35.4%) occurred within the first 30 days, 20 (17.7%) between 30 days and 6 months, 16 (14.2%) between 6 months and 1 year and 37 (32.7%) between 1 and 2 years post-transplantation. Using the Kaplan-Meier method, estimated graft survival was 98.2% (95% confidence interval [CI] 97.6, 98.7) at 30 days, 97.3% (95% CI 96.5, 97.9) at 6 months, 96.6% (95% CI 95.7, 97.3) at 1 year and 94.8% (95% CI 93.8, 95.7) at 2 years.

Unadjusted survival analysis using Kaplan-Meier estimates identified recipients with PVD and obesity as having worse graft survival at 2 years post-transplantation (Figure 5.3. and 5.4.). Graft survival for patients with PVD was 89.0% compared with 95.0% for patients who did not have PVD at the time of transplantation (p=0.016). The risk of graft failure among PVD patients appeared to be highest within the first 30 days following transplantation, which is when 75% of graft failures occurred. This is demonstrated in the Kaplan-Meier plot by the initial sharp reduction in graft survival, followed by a flatter curve. Graft survival at 2 years among obese patients was 92.9% compared with 95.3% in non-obese patients (p=0.045). Examination of the Kaplan-Meier curve for obesity demonstrates a more gradual decline in graft survival over the 2 year period. Among obese patients, 53% of graft failures occurred within the first year and 47% within the second year post-transplantation.

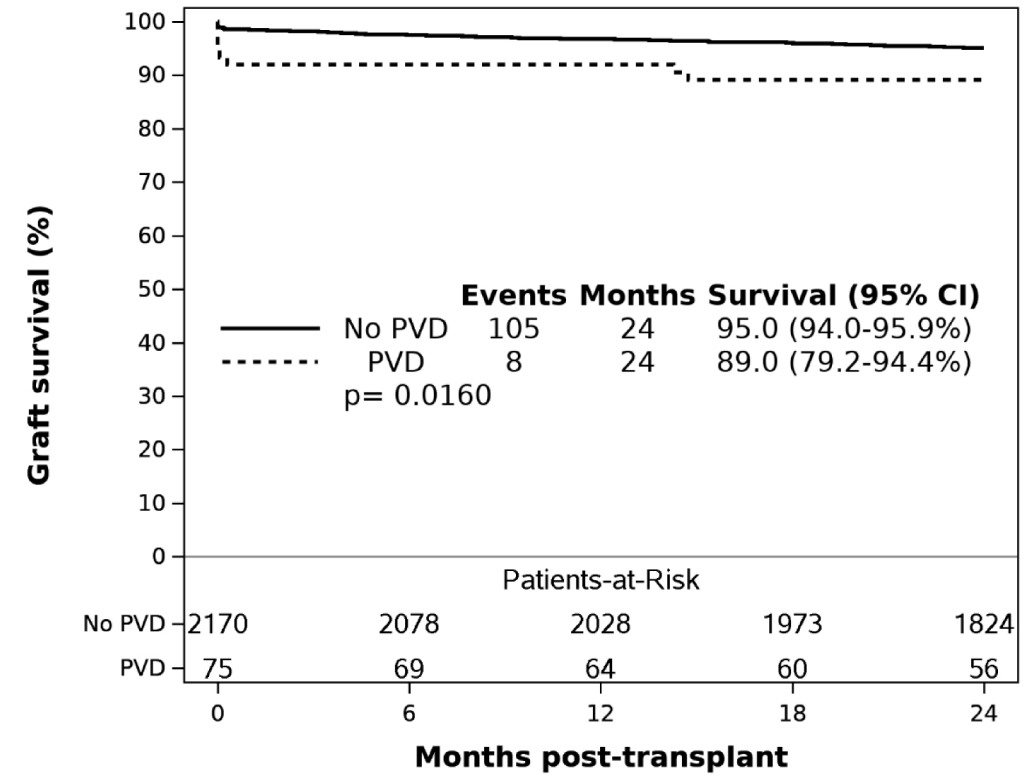

Figure 5.3. Kaplan–Meier survival plot for effect of PVD on 2 year graft survival

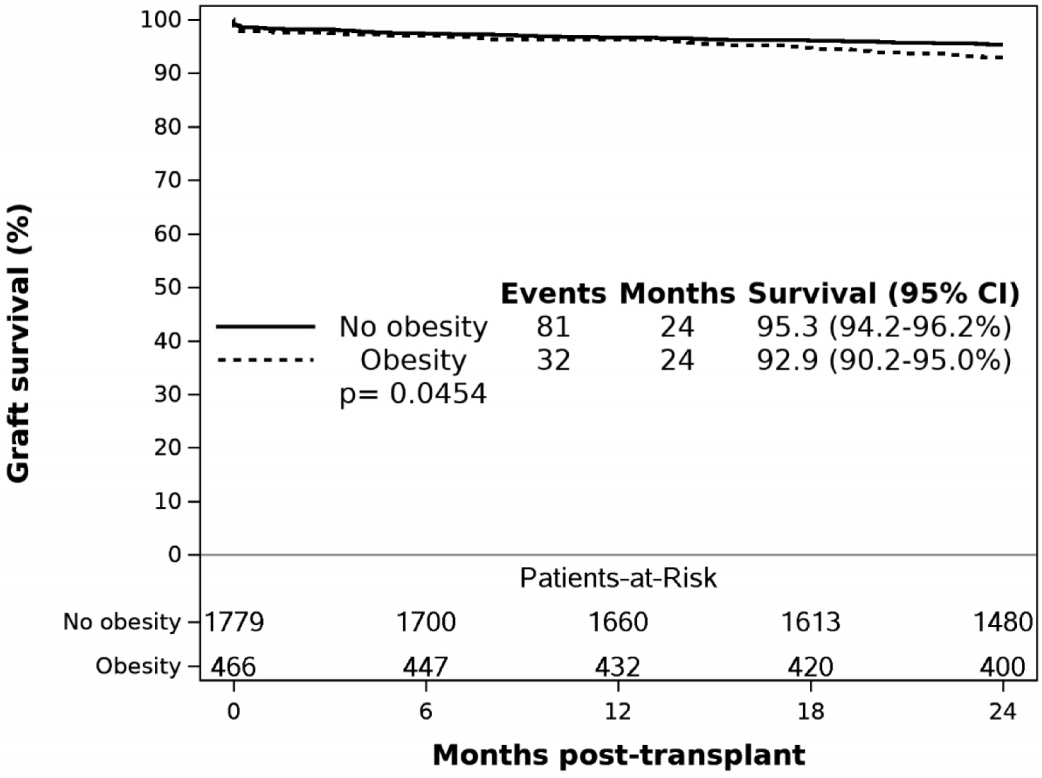

Figure 5.4. Kaplan–Meier survival plot for effect of obesity on 2 year graft survival

The association of each recipient comorbidity (Table 5.6), as well as recipient (Table 5.7), donor and transplant variables (Table 5.8) with graft survival was examined using univariable Cox regression. Recipient comorbidities that were significantly associated with 2 year graft survival on univariable analysis included heart failure, PVD and obesity. However, all comorbidities were considered for inclusion in the multivariable model. Other covariates that were considered in the multivariable modelling process based on the univariable results and *a priori* decisions included recipient age, recipient ethnicity, time on dialysis, previous transplantation, highly sensitised, donor age, HLA MM level, transplant type and CIT.

Table 5.6. Univariable Cox regression analysis of recipient comorbidities affecting 2 year graft survival

Variables	HR	[95% CI]	p-value
Comorbidities			
Diabetes	1.32	[0.86, 2.03]	0.211
Ischaemic heart disease	0.81	[0.39, 1.66]	0.562
Heart failure	2.34	[1.03, 5.32]	0.043
Atrial fibrillation	1.62	[0.51, 5.09]	0.413
Cardiac valve replacement	.	.	.
Pacemaker	1.38	[0.19, 9.85]	0.750
Cerebrovascular disease	1.75	[0.88, 3.45]	0.109
Peripheral vascular disease	2.38	[1.16, 4.88]	0.018
Abdominal aortic aneurysm	.	.	.
Chronic respiratory disease	1.57	[0.88, 2.80]	0.126
Chronic liver disease	1.56	[0.50, 4.92]	0.445
Blood borne viruses	1.60	[0.59, 4.34]	0.356
Malignancy	0.82	[0.36, 1.86]	0.628
Mental illness	1.55	[0.81, 2.96]	0.189
Dementia	.	.	.
BMI (kg/m^2)			
Underweight (<18.5)	1.60	[0.49, 5.22]	0.440
Normal (18.5 – 24.9)	1 [ref]		
Overweight (25.0 – 29.9)	1.38	[0.86, 2.20]	0.185
Obese (≥30.0)	1.89	[1.14, 3.11]	0.013

CI; confidence interval, HR; hazard ratio, ref; reference. (.) number is 0 or too small to calculate

Table 5.7. Univariable Cox regression analysis of recipient factors affecting 2 year graft survival

Variables	HR	[95% CI]	p-value
Age (per 10 year increase)	1.00	[0.87, 1.15]	0.996
Gender			
Male	1 [ref]		
Female	0.82	[0.55, 1.21]	0.315
Ethnicity			
White	1 [ref]		
Asian	1.01	[0.53, 1.95]	0.969
Black	2.38	[1.38, 4.11]	0.002
Other	0.60	[0.08, 4.29]	0.609
Primary renal disease			
Polycystic kidney disease	1 [ref]		
Diabetic nephropathy	1.49	[0.71, 3.13]	0.287
Glomerulonephritis	1.41	[0.72, 2.77]	0.320
Pyelonephritis	1.24	[0.56, 2.76]	0.596
Hypertensive nephropathy	1.56	[0.62, 3.97]	0.349
Renal vascular disease	1.45	[0.33, 6.49]	0.625
Other	1.77	[0.88, 3.58]	0.111
Uncertain	1.47	[0.67, 3.23]	0.332
Time on dialysis			
Pre-emptive	1 [ref]		
0 - 3 years	1.25	[0.67, 2.32]	0.483
> 3 years	2.88	[1.62, 5.14]	0.0003
Smoking status			
Non-smoker	1 [ref]		
Smoker	1.02	[0.56, 1.84]	0.960
Ex-smoker	0.92	[0.60, 1.43]	0.722
Previous transplant	1.71	[1.07, 2.73]	0.024
Highly sensitised (cRF≥85%)	2.04	[1.27, 3.27]	0.003
Recipient blood group			
A	1 [ref]		
B	0.70	[0.34, 1.43]	0.329
AB	0.83	[0.30, 2.31]	0.720
O	1.23	[0.83, 1.83]	0.307

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Table 5.8. Univariable Cox regression analysis of donor and transplant factors affecting 2 year graft survival

Variables	HR	[95% CI]	p-value
Donor variables			
Donor Age (per 10 year increase)	1.21	[1.06, 1.39]	0.004
Donor Gender			
Male	1 [ref]		
Female	1.07	[0.74, 1.54]	0.728
Donor Ethnicity			
White	1 [ref]		
Asian	0.51	[0.13, 2.06]	0.344
Black	1.15	[0.37, 3.64]	0.807
Other	1.25	[0.31, 5.07]	0.754
Donor BMI (kg/m^2)			
Underweight (<18.5)	.	.	.
Normal (18.5 – 24.9)	1 [ref]		
Overweight (25.0 – 29.9)	1.04	[0.68, 1.58]	0.873
Obese (≥30.0)	1.03	[0.61, 1.75]	0.908
Donor blood group			
A	1 [ref)		
B	0.52	[0.22, 1.23]	0.138
AB	1.27	[0.46, 3.56]	0.647
O	1.10	[0.74, 1.62]	0.651
Transplant variables			
HLA MM level			
1	1 [ref]		
2	2.32	[1.02, 5.28]	0.044
3	1.95	[0.89, 4.26]	0.096
4	1.20	[0.49, 2.93]	0.696
Transplant type			
Living donor KO	1 [ref]		
Deceased donor KO	2.05	[1.32, 3.19]	0.001
SPK	0.84	[0.29, 2.41]	0.748
CIT (per hour)	1.05	[1.02, 1.08]	0.001

CI; confidence interval, HR; hazard ratio, ref; reference
(.) number is 0 or too small to calculate

After adjustment for relevant confounding factors in the multivariable model (Table 5.9.), recipient PVD (hazard ratio; HR 2.77, 95% CI 1.33, 5.79, p=0.007) and obesity (BMI≥30 kg/m^2) (HR 1.96, 95% CI 1.18, 3.27, p=0.009, compared with BMI 18.5-24.9 kg/m^2) were confirmed to be independent risk factors for

graft loss within 2 years. In the modelling process, the obesity variable was explored both as a continuous BMI variable (linear, quadratic and log transformations) and also as a categorical variable. Categories considered included BMI ≥30 kg/m^2, ≥35 kg/m^2 and ≥40 kg/m^2, both as dichotomous yes/no variable and also as a variable containing the categories <18.5 kg/m^2, 18.5 - 24.9 kg/m^2, 25.0 - 29.9 kg/m^2. The variable categorised as 4 BMI groups as shown in Table 5.9 produced the best fit in the multivariable model and allowed comparison of obese patients to patients with a "normal" BMI. There was a trend for increasing risk of graft failure with further categorisation of BMI ≥35 kg/m^2 and ≥40 kg/m^2, however the results did not reach statistical significance, likely due to insufficient numbers. Other variables found to be significant confounders were included in the multivariable model. Increasing recipient age was associated with better graft survival (HR 0.83 per 10 year increase, 95% CI 0.69, 0.99, p=0.038). Black compared to White recipient ethnicity adversely affected graft survival, and although this did not quite reach statistical significance (HR 1.68, 95% CI 0.92, 3.07, p=0.089), the ethnicity variable was kept in the model due to its clinical significance. Pre-transplant time on dialysis had a negative effect on graft survival, but this was only apparent after 3 years on dialysis (> 3 years on dialysis versus pre-emptive transplant, HR 2.24, 95% CI 1.10, 4.59, p=0.027), hence the variable was categorised accordingly to reduce the number of degrees of freedom in the model. A high level of recipient sensitisation (cRF≥85%) increased the risk of graft failure (HR 2.17, 95% CI 1.28, 3.68, p=0.004). The previous transplantation variable was univariably significant for worse graft survival but was not significant in the multivariable model. This can be explained by its strong correlation with the highly sensitised variable (Cramer's V

coefficient=0.499). Adding previous transplantation to the multivariable model did not reduce the effect of the highly sensitised variable. Increasing donor age (HR 1.24 per 10 year increase, 95% CI 1.06, 1.45, p=0.009) and poorer HLA MM level were also associated with worse graft survival. Deceased donor KO transplants did worse than living donor KO transplants (HR 1.97, 95% CI 1.13, 3.44, p=0.017), whereas SPK transplants showed no significant difference to living donor transplants. Increasing CIT was univariably associated with worse graft survival, but adding it to the multivariable model caused CIT, as well as the transplant type variable to lose significance. This implies that the worse graft survival among deceased donor transplants compared with living donor transplants is partly explained by increased CIT (median CIT 14.5 vs 3.3 hours, respectively). Despite a median CIT of 13.6 hours, SPK transplants did not have significantly worse graft survival than living donor kidney transplants. Of note, there was no difference in graft survival for transplants from donors after circulatory death compared with donors after brain death for deceased KO or SPK transplants, therefore all deceased donors were considered together for each type of transplant. Including transplant centre as a random effect in the multivariable model showed no evidence for a centre effect on graft survival (change in -2 log-likelihood p=0.404).

Table 5.9. Multivariable Cox regression analysis of factors affecting 2 year graft survival

Variables	HR	[95% CI]	p-value
Recipient comorbidities			
Peripheral vascular disease	2.77	[1.33, 5.79]	0.007
BMI			
Underweight (<18.5)	1.65	[0.50, 5.49]	0.412
Normal (18.5 - 24.9)	1 [ref]		
Overweight (25.0 - 29.9)	1.44	[0.89, 2.33]	0.133
Obese (≥30.0)	1.96	[1.18, 3.27]	0.009
Other variables			
Recipient age (per 10 yr increase)	0.83	[0.69, 0.99]	0.038
Recipient ethnicity			
White	1 [ref]		
Asian	0.83	[0.41, 1.67]	0.604
Black	1.68	[0.92, 3.07]	0.089
Other	0.50	[0.07, 3.63]	0.494
Time on dialysis			
Pre-emptive	1 [ref]		
0 - 3 years	1.24	[0.60, 2.56]	0.559
> 3 years	2.24	[1.10, 4.59]	0.027
Highly sensitised (cRF≥85%)	2.17	[1.28, 3.68]	0.004
Donor age (per 10 year increase)	1.24	[1.06, 1.45]	0.009
Transplant type			
Living donor KO	1 [ref]		
Deceased donor KO	1.97	[1.13, 3.44]	0.017
SPK	1.07	[0.31, 3.73]	0.920
HLA MM level			
1	1 [ref]		
2	2.39	[1.02, 5.61]	0.044
3	1.99	[0.88, 4.51]	0.097
4	1.88	[0.69, 5.09]	0.211

CI; confidence interval, HR; hazard ratio, ref; reference

5.3.3. Impact of recipient comorbidity on 2 year patient survival

Patient survival data were missing for 4 of 2250 kidney transplant recipients in the study. Of the remaining 2246 patients included in the analysis, 76 (3.4%) patients died within the 2 year follow up period, (69 of 76 [90.8%] deaths were with a functioning graft), 268 (11.9%) were censored at last follow-up and 1902 (84.7%) were censored at 2 years. Of the 268 patients censored at last follow-up, median censoring time was 518.5 days (IQR 244 - 691.5 days). There were 2 (2.6%) deaths within the first 30 days, 24 (31.6%) between 30 days and 6 months, 15 (19.7%) between 6 months and 1 year and 35 (46.1%) between 1 and 2 years post-transplantation. Using the Kaplan-Meier method, overall patient survival was 99.9% (95% CI 99.6 - 99.9) at 30 days, 98.8% (95% CI 98.3 - 99.2) at 6 months, 98.1% (95% CI 97.5 - 98.6) at 1 year and 96.5% (95% CI 95.6 - 97.2) at 2 years.

Kaplan-Meier survival plots (unadjusted) demonstrated significantly worse 2 year patient survival for those with diabetes (Figure 5.5.), heart failure (Figure 5.6.), a pacemaker (Figure 5.7.), CVD (Figure 5.8.), PVD (Figure 5.9.) and CLD (Figure 5.10.), compared to patients without these comorbidities.

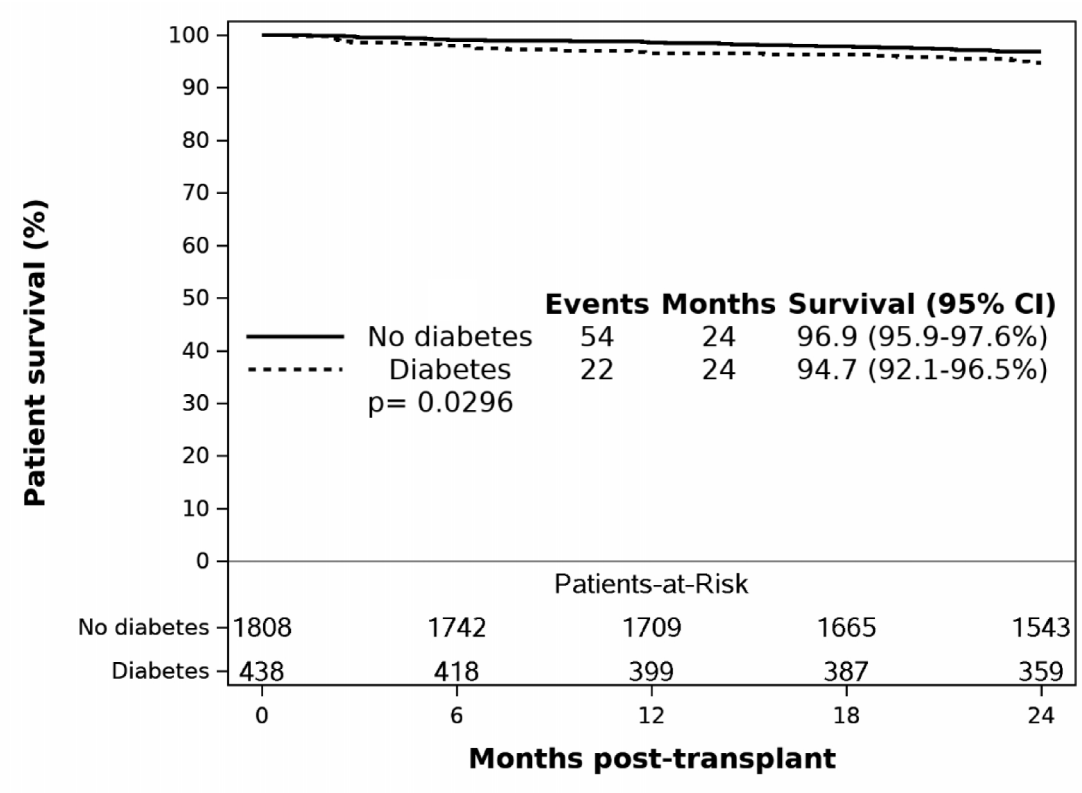

Figure 5.5. Kaplan–Meier survival plot for effect of diabetes on 2 year patient survival

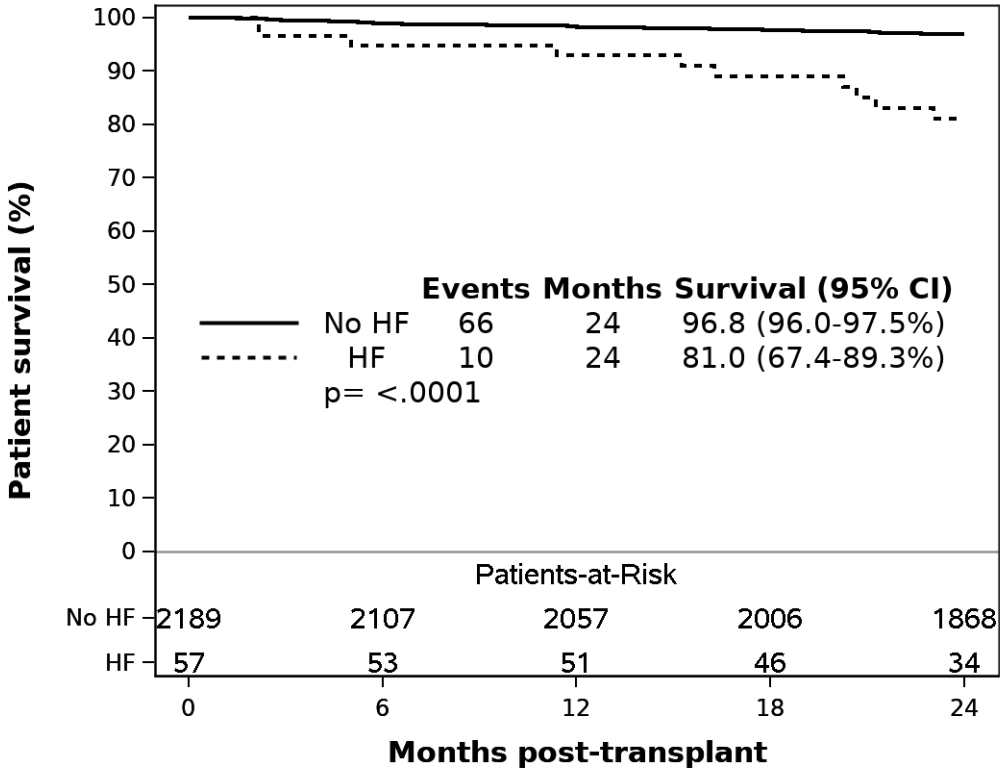

Figure 5.6. Kaplan–Meier survival plot for effect of heart failure (HF) on 2 year patient survival

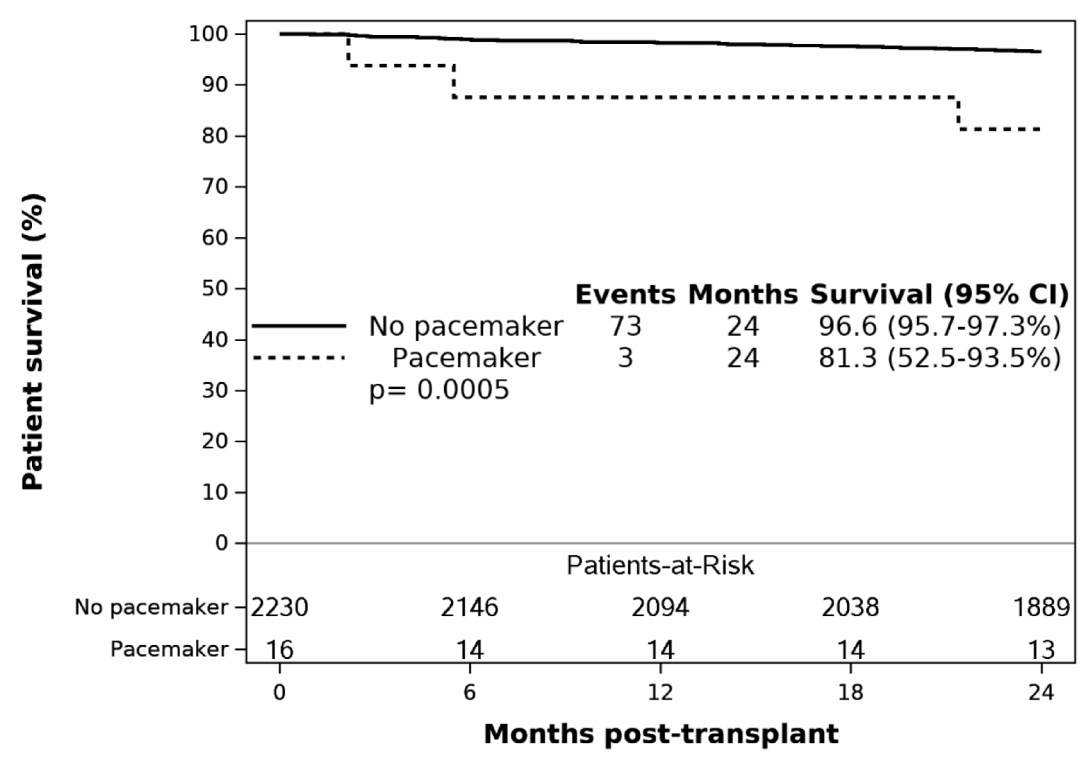

Figure 5.7. Kaplan–Meier survival plot for effect of pacemaker on 2 year patient survival

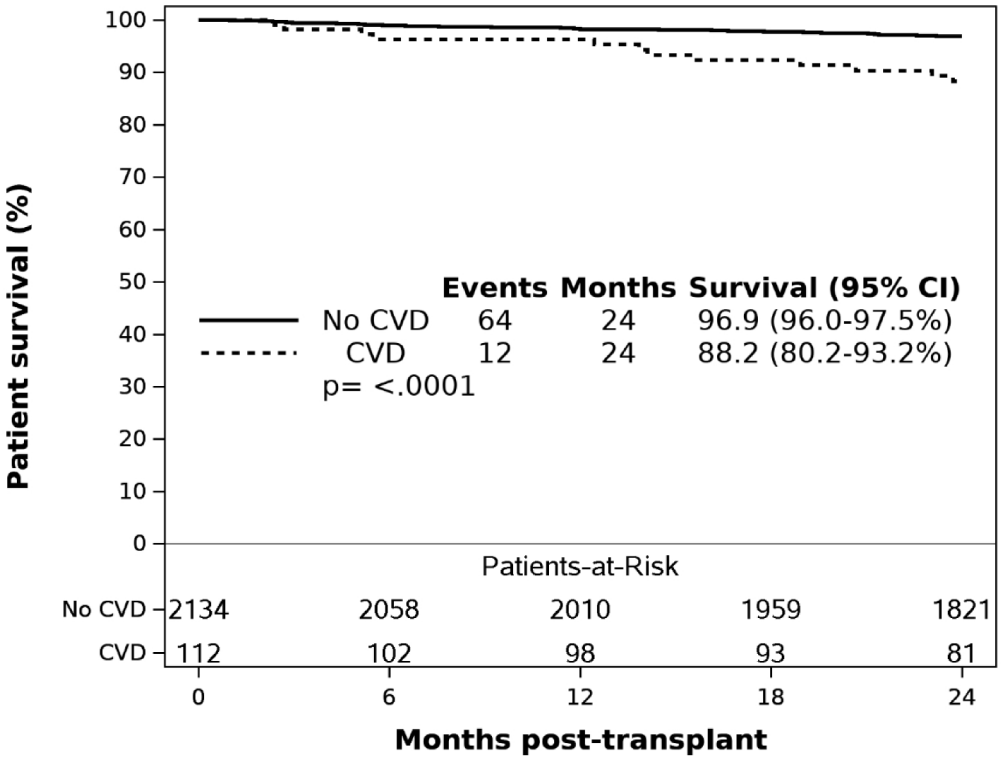

Figure 5.8. Kaplan–Meier survival plot for effect of cerebrovascular disease (CVD) on 2 year patient survival

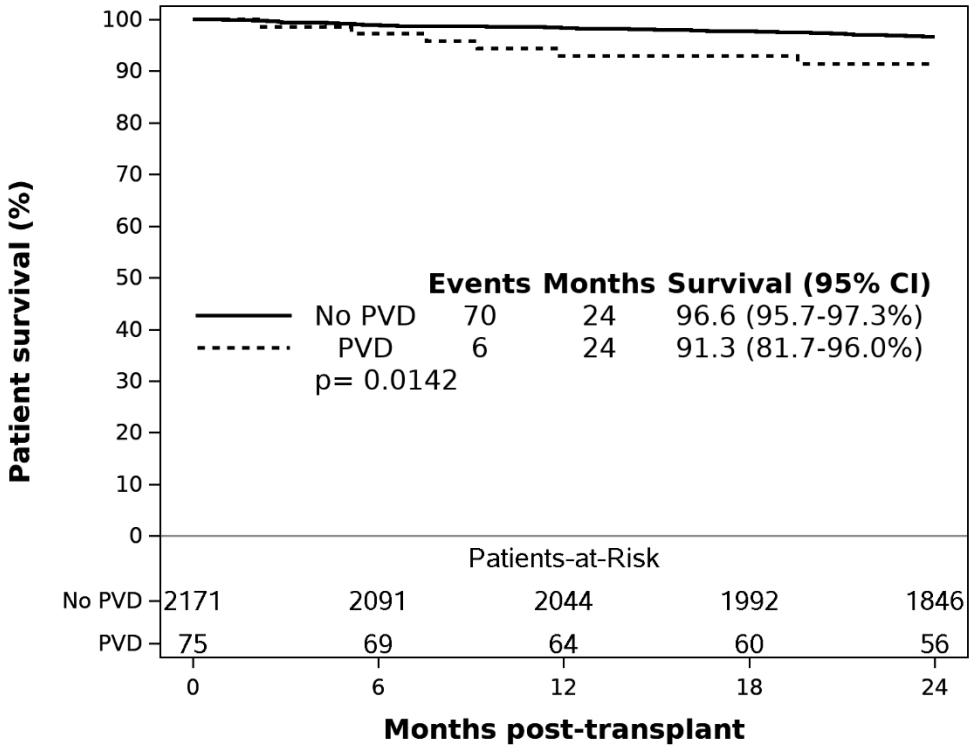

Figure 5.9. Kaplan–Meier survival plot for effect of peripheral vascular disease (PVD) on 2 year patient survival

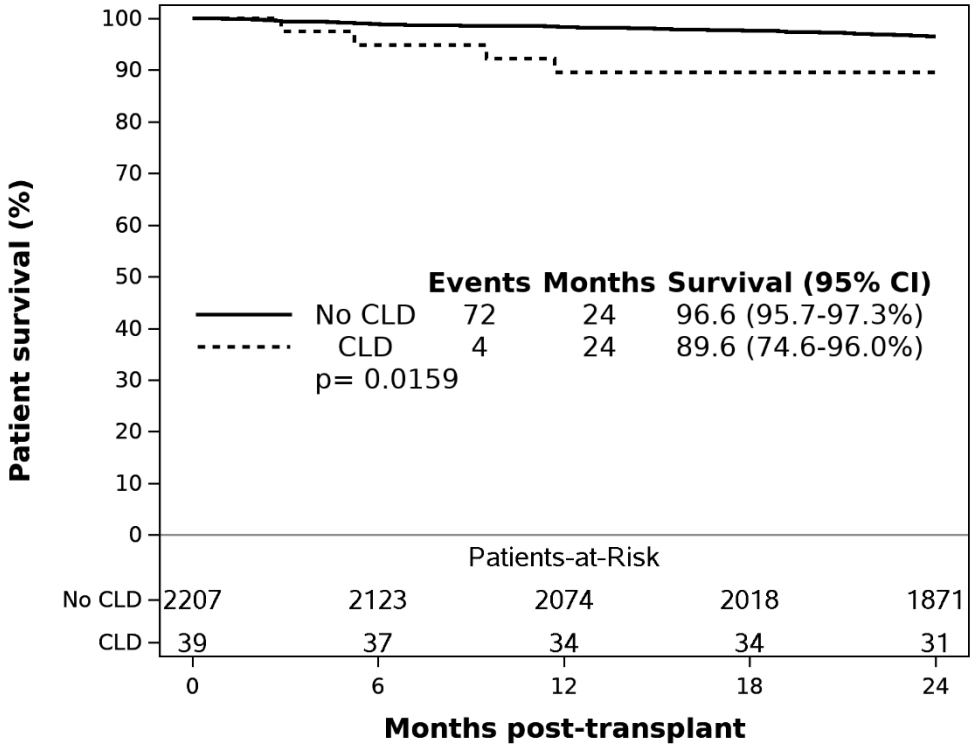

Figure 5.10. Kaplan–Meier survival plot for effect of chronic liver disease (CLD) on 2 year patient survival

Univariable Cox regression was used to analyse the impact of recipient comorbidity (Table 5.10) as well as other recipient (Table 5.11), donor and transplant (Table 5.12) variables on 2 year patient survival after transplantation. Recipient comorbidities that were significantly associated with 2 year patient survival on univariable analysis included diabetes, heart failure, pacemaker, CVD, PVD and CLD. However, all recipient comorbidities were considered for inclusion in the multivariable model. Other covariates that were considered in the multivariable modelling process based on the univariable results and *a priori* decisions included recipient age, primary renal disease, time on dialysis, donor age, donor gender, donor BMI, donor blood group, HLA MM level, transplant type and CIT.

Table 5.10. Univariable Cox regression analysis of recipient comorbidities affecting 2 year patient survival

Variables	HR	[95% CI]	p-value
Diabetes	1.72	[1.05, 2.83]	0.032
Ischaemic heart disease	1.43	[0.71, 2.87]	0.315
Heart failure	6.56	[3.38, 12.77]	<0.0001
Atrial fibrillation	1.61	[0.40, 6.56]	0.506
Cardiac valve replacement	1.55	[0.22, 11.17]	0.662
Pacemaker	6.45	[2.03, 20.46]	0.002
Cerebrovascular disease	3.86	[2.08, 7.15]	<0.0001
Peripheral vascular disease	2.75	[1.20, 6.33]	0.017
Abdominal aortic aneurysm	4.92	[0.69, 35.41]	0.113
Chronic respiratory disease	1.04	[0.45, 2.40]	0.922
Chronic liver disease	3.21	[1.17, 8.79]	0.023
Blood borne viruses	0.59	[0.08, 4.22]	0.596
Malignancy	1.70	[0.82, 3.54]	0.154
Mental illness	1.13	[0.46, 2.79]	0.796
Dementia	.	.	.
BMI			
Underweight (<18.5)	0.56	[0.08, 4.07]	0.563
Normal (18.5 - 24.9)	1 [ref]		
Overweight (25.0 - 29.9)	0.88	[0.51, 1.50]	0.637
Obese (≥30.0)	0.85	[0.44, 1.62]	0.613

CI; confidence interval, HR; hazard ratio, ref; reference.

(.) number is 0 or too small to calculate

Table 5.11. Univariable Cox regression analysis of recipient factors affecting 2 year patient survival

Variables	HR	[95% CI]	p-value
Age (per 10 year increase)	1.76	[1.44, 2.15]	<0.0001
Gender			
Male	1 [ref]		
Female	0.82	[0.51, 1.32]	0.407
Ethnicity			
White	1 [ref]		
Asian	0.80	[0.35, 1.85]	0.603
Black	0.85	[0.31, 2.33]	0.752
Other	.	.	.
Primary renal disease			
Polycystic kidney disease	1 [ref]		
Diabetic nephropathy	4.28	[1.61, 11.41]	0.004
Glomerulonephritis	1.96	[0.72, 5.34]	0.190
Pyelonephritis	1.49	[0.45, 4.88]	0.511
Hypertensive nephropathy	3.83	[1.22, 12.07]	0.022
Renal vascular disease	3.57	[0.69, 18.38]	0.129
Other	2.93	[1.06, 8.05]	0.038
Uncertain	1.36	[0.39, 4.69]	0.628
Time on dialysis			
Pre-emptive	1 [ref]		
0 - 3 years	1.19	[0.52, 2.73]	0.674
> 3 years	3.96	[1.87, 8.36]	0.0003
Smoking status			
Non-smoker	1 [ref]		
Smoker	1.31	[0.68, 2.55]	0.424
Ex-smoker	0.74	[0.41, 1.32]	0.305
Previous transplant	1.07	[0.55, 2.08]	0.850
Highly sensitised (cRF≥85%)	1.37	[0.7, 2.66]	0.358
Recipient blood group			
A	1 [ref]		
B	1.15	[0.58, 2.28]	0.694
AB	0.82	[0.25, 2.69]	0.746
O	0.86	[0.52, 1.42]	0.559

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Table 5.12. Univariable Cox regression analysis of donor and transplant factors affecting 2 year patient survival

Variables	HR	[95% CI]	p-value
Donor variables			
Donor Age (per 10 year increase)	1.40	[1.18, 1.66]	0.0001
Donor Gender			
Male	1 [ref]		
Female	1.70	[1.07, 2.71]	0.024
Donor Ethnicity			
White	1 [ref]		
Asian	0.76	[0.19, 3.11]	0.705
Black	1.71	[0.54, 5.45]	0.361
Other	0.94	[0.13, 6.77]	0.951
Donor BMI (kg/m^2)			
Underweight (<18.5)	.	.	.
Normal (18.5 – 24.9)	1 [ref]		
Overweight (25.0 – 29.9)	1.57	[0.90, 2.75]	0.115
Obese (≥30.0)	2.39	[1.30, 4.39]	0.005
Donor blood group			
A	1 [ref]		
B	0.71	[0.32, 1.59]	0.405
AB	1.09	[0.34, 3.55]	0.884
O	0.62	[0.38, 1.01]	0.056
Transplant variables			
HLA MM level			
1	1 [ref]		
2	0.48	[0.22, 1.05]	0.064
3	0.63	[0.33, 1.18]	0.146
4	0.64	[0.30, 1.34]	0.237
Transplant type			
Living donor KO	1 [ref]		
Deceased donor KO	2.22	[1.27, 3.87]	0.005
SPK	1.72	[0.63, 4.69]	0.291
CIT (per hour)	1.05	[1.02, 1.09]	0.002

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Recipient comorbidities found to be independent risk factors for patient death after adjustment for confounding factors in the multivariable model (Table 5.13) included heart failure (HR 3.37, 95% CI 1.69, 6.72, p=0.0005), CVD (HR 2.51, 95% CI 1.32, 4.78, p=0.005) and CLD (HR 3.97, 95% CI 1.43, 11.04,

p=0.008). The diabetes variable which was significant on univariable analysis was explored in several different ways;

a) any diagnosis of diabetes

b) diabetes as a comorbidity only (excluding diabetes as primary renal disease)

c) diabetes as primary renal disease only

d) type 1 diabetes

e) type 2 diabetes

Diabetes as a primary renal disease was the only diabetes variable that was significant after adjustment for all other confounders in the multivariable model, perhaps suggesting that the severity of the disease is the most important factor for patient survival. Compared with polycystic kidney disease, diabetic nephropathy (HR 4.20, 95% CI 1.51, 11.68, p=0.006), glomerulonephritis (HR 2.78, 95% CI 1.01, 7.62, p=0.048) and hypertensive nephropathy (HR 4.25, 95% CI 1.34, 13.48, p=0.014) as a primary renal disease were associated with significantly worse patient survival. Other variables significant in the multivariable model included recipient age (HR 1.71 per 10 year increase, 95% CI 1.38, 2.13, p<0.0001) and pre-transplant time on dialysis (> 3 years on dialysis versus pre-emptive transplant, HR 2.88, 95% CI 1.31, 6.33, p=0.009). As with graft survival, the negative effect of dialysis on patient survival was only significant for over 3 years on dialysis after adjustment for confounding factors. The type of transplant did not significantly affect patient survival. There was no evidence for a centre effect on patient survival (change in -2 log-likelihood p=0.984) upon adding transplant centre as a random effect in the model.

Table 5.13. Multivariable Cox regression analysis of factors affecting 2 year patient survival			
Variables	**HR**	**[95% CI]**	**p-value**
Recipient comorbidities			
Heart failure	3.37	[1.69, 6.72]	0.0005
Cerebrovascular disease	2.51	[1.32, 4.78]	0.005
Chronic liver disease	3.97	[1.43, 11.04]	0.008
Other variables			
Recipient age (per 10 yr increase)	1.71	[1.38, 2.13]	<0.0001
Primary renal disease			
Polycystic kidney disease	1 [ref]		
Diabetic nephropathy	4.20	[1.51, 11.68]	0.006
Glomerulonephritis	2.78	[1.01, 7.62]	0.048
Pyelonephritis	2.30	[0.69, 7.62]	0.174
Hypertensive nephropathy	4.25	[1.34, 13.48]	0.014
Renal vascular disease	3.25	[0.62, 16.90]	0.162
Other	4.26	[1.54, 11.82]	0.005
Uncertain	1.41	[0.41, 4.89]	0.589
Time on dialysis			
Pre-emptive	1 [ref]		
0 - 3 years	1.04	[0.45, 2.40]	0.929
> 3 years	2.88	[1.31, 6.33]	0.009
Transplant type			
Living donor KO	1 [ref]		
Deceased donor KO	1.10	[0.61, 1.99]	0.755
SPK	1.75	[0.55, 5.57]	0.343

CI; confidence interval, HR; hazard ratio, ref; reference

5.3.4. Impact of recipient comorbidity on 2 year transplant survival

A further analysis of a combined "transplant survival" outcome was undertaken, where transplant failure was defined as the earliest of graft failure or patient death. The outcome variable was missing for 5 of 2250 patients, thus the analysis was conducted on a cohort of 2245 patients. There were 182 (8.1%) transplant failures within the 2 year follow up period (113 graft failures and 69 deaths), 183 (8.2%) patients were censored at last follow-up and 1880 (83.7%) patients were censored at 2 years. Of the 183 patients censored at last follow-up, median censoring time was 670 days, interquartile

range 365 - 707 days. In all, 42 (23.1%) transplant failures occurred within the first 30 days, 38 (20.9%) between 30 days and 6 months, 30 (16.5%) between 6 months and 1 year and 72 (39.6%) between 1 and 2 years post-transplantation. Using the Kaplan-Meier method, transplant survival was 98.1% (95%CI 97.5 - 98.6) at 30 days, 96.4% (95%CI 95.5 - 97.1) at 6 months, 95.1% (95%CI 94.1 - 95.9) at 1 year and 91.7% (95%CI 90.5 - 92.8) at 2 years.

Univariable Cox regression analysis for 2 year transplant survival is shown in Table 5.14, 5.15 and 5.16. Diabetes, heart failure, CVD and PVD were significantly associated with transplant survival on univariable analysis. All recipient comorbidities were considered for inclusion in the multivariable model. Other variables that were also considered for inclusion in the multivariable model included recipient age, recipient ethnicity, primary renal disease, time on dialysis, previous transplantation, highly sensitised, donor age, donor gender, donor BMI, transplant type and CIT.

Table 5.14. Univariable Cox regression analysis of recipient comorbidities affecting 2 year transplant survival

Variables	HR	[95% CI]	p-value
Diabetes	1.47	[1.05-2.05]	0.024
Ischaemic heart disease	1.21	[0.75-1.94]	0.437
Heart failure	3.71	[2.19-6.29]	<0.0001
Atrial fibrillation	1.30	[0.48-3.51]	0.602
Cardiac valve replacement	0.63	[0.09-4.47]	0.640
Pacemaker	2.55	[0.81-7.97]	0.108
Cerebrovascular disease	2.46	[1.54-3.91]	0.0001
Peripheral vascular disease	2.18	[1.21-3.91]	0.009
Abdominal aortic aneurysm	1.99	[0.28-14.16]	0.494
Chronic respiratory disease	1.30	[0.80-2.11]	0.291
Chronic liver disease	1.92	[0.85-4.34]	0.115
Blood borne viruses	0.96	[0.36-2.58]	0.933
Malignancy	1.19	[0.69-2.04]	0.542
Mental illness	1.30	[0.75-2.24]	0.348
Dementia	.	.	.
BMI			
Underweight (<18.5)	1.10	[0.40-3.03]	0.854
Normal (18.5 - 24.9)	1 [ref]		
Overweight (25.0 - 29.9)	1.13	[0.79-1.61]	0.500
Obese (≥30.0)	1.36	[0.92-2.02]	0.124

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Table 5.15. Univariable Cox regression analysis of recipient factors affecting 2 year transplant survival

Variables	HR	[95% CI]	p-value
Age (per 10 year increase)	1.21	[1.08-1.36]	0.0008
Gender			
Male	1 [ref]		
Female	0.82	[0.60-1.11]	0.199
Ethnicity			
White	1 [ref]		
Asian	0.95	[0.57-1.58]	0.832
Black	1.86	[1.17-2.97]	0.009
Other	0.35	[0.05-2.48]	0.293
Primary renal disease			
Polycystic kidney disease	1 [ref]		
Diabetic nephropathy	2.39	[1.33-4.30]	0.004
Glomerulonephritis	1.59	[0.89-2.83]	0.115
Pyelonephritis	1.40	[0.71-2.74]	0.331
Hypertensive nephropathy	2.52	[1.25-5.10]	0.010
Renal vascular disease	2.19	[0.73-6.55]	0.161
Other	2.18	[1.21-3.93]	0.009
Uncertain	1.62	[0.83-3.16]	0.154
Time on dialysis			
Pre-emptive	1 [ref]		
0 - 3 years	1.18	[0.72-1.95]	0.511
> 3 years	3.12	[1.97-4.94]	<0.0001
Smoking status			
Non-smoker	1 [ref]		
Smoker	1.30	[0.64, 1.65]	0.905
Ex-smoker	0.88	[0.62, 1.25]	0.479
Previous transplant	1.52	[1.04-2.22]	0.030
Highly sensitised (cRF≥85%)	1.86	[1.27-2.73]	0.001
Recipient blood group			
A	1 [ref]		
B	0.91	[0.56, 1.50]	0.716
AB	0.73	[0.32, 1.68]	0.459
O	1.05	[0.77, 1.44]	0.750

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Table 5.16. Univariable Cox regression analysis of donor and transplant factors affecting 2 year transplant survival			
Variables	**HR**	**[95% CI]**	**p-value**
Donor variables			
Donor Age (per 10 year increase)	1.26	[1.13-1.40]	<0.0001
Donor Gender			
Male	1 [ref]		
Female	1.28	[0.96-1.70]	0.099
Donor Ethnicity			
White	1 [ref]		
Asian	0.62	[0.23-1.67]	0.343
Black	1.40	[0.62-3.17]	0.414
Other	1.14	[0.37-3.58]	0.818
Donor BMI (kg/m^2)			
Underweight (<18.5)	.	.	.
Normal (18.5 - 24.9)	1 [ref]		
Overweight (25.0 - 29.9)	1.22	[0.87-1.71]	0.255
Obese (≥30.0)	1.46	[0.99-2.17]	0.059
Donor blood group			
A	1 [ref]		
B	0.62	[0.35, 1.12]	0.116
AB	1.01	[0.46, 2.42]	0.906
O	0.86	[0.63, 1.17]	0.339
Transplant variables			
HLA MM level			
1	1 [ref]		
2	1.07	[0.63-1.83]	0.795
3	1.08	[0.67-1.74]	0.763
4	0.84	[0.48-1.47]	0.537
Transplant type			
Living donor KO	1 [ref]		
Deceased donor KO	2.01	[1.42, 2.85]	<0.0001
SPK	1.18	[0.57, 2.42]	0.659
CIT (per hour)	1.05	[1.03, 1.07]	<0.0001

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Recipient comorbidities that independently increased the risk of transplant failure after adjustment for relevant factors in the multivariable model (Table 5.17) included heart failure (HR 2.32, 95% CI 1.35, 3.99, p=0.002) and CVD (HR 1.65, 95% CI 1.01, 2.70, p=0.044). Other variables significant in the

multivariable transplant survival model included a primary renal disease of diabetic nephropathy (HR 2.42, 95% CI 1.29, 4.56, p=0.006) and hypertensive nephropathy (HR 2.22, 95% CI 1.08, 4.56, p=0.030) compared with polycystic kidney disease, pre-transplant time on dialysis (> 3 years on dialysis versus pre-emptive transplant, HR 2.11, 95% CI 1.29, 3.45, p0.003), donor age (HR 1.16 per 10 year increase, 95% CI 1.03, 1.31, p=0.0014) and highly sensitised (HR 1.54, 95% CI 1.02, 2.32, p=0.041). Recipient age and transplant type were included in the model but did not show significant effects on transplant survival. Including transplant centre as a random effect in the model did not show any evidence for between-centre variation in transplant survival (change in -2 log likelihood p=0.680).

Table 5.17. Multivariable Cox regression analysis of factors affecting 2 year transplant survival			
Variables	**HR**	**[95% CI]**	**p-value**
Recipient comorbidities			
Heart failure	2.32	1.35-3.99]	0.002
Cerebrovascular disease	1.65	[1.01-2.70]	0.044
Other variables			
Recipient age (per 10 yr increase)	1.08	[0.95, 1.23]	0.250
Primary renal disease			
Polycystic kidney disease	1 [ref]		
Diabetic nephropathy	2.42	[1.29, 4.56]	0.006
Glomerulonephritis	1.72	[0.96, 3.08]	0.068
Pyelonephritis	2.45	[0.73, 2.89]	0.286
Hypertensive nephropathy	2.22	[1.08, 4.56]	0.030
Renal vascular disease	2.09	[0.70, 6.25]	0.190
Other	2.32	[1.28, 4.23]	0.006
Uncertain	1.49	[0.76, 2.93]	0.247
Time on dialysis			
Pre-emptive	1 [ref]		
0 - 3 years	1.01	[0.61, 1.68]	0.969
> 3 years	2.11	[1.29, 3.45]	0.003
Highly sensitised (cRF≥85%)	1.54	[1.02, 2.32]	0.041
Donor age (per 10 year increase)	1.16	[1.03, 1.31]	0.014
Transplant type			
Living donor KO	1 [ref]		
Deceased donor KO	1.35	[0.92, 1.97]	0.125
SPK	1.11	[0.49, 2.55]	0.801

CI; confidence interval, HR; hazard ratio, ref; reference

Several of the variables that were significant risk factors for graft survival (PVD, obesity, recipient age, recipient ethnicity, transplant type, HLA MM level) and patient survival (CLD, recipient age) were not found to be significant in the model for transplant survival. A comparison of the multivariable models for graft, patient and transplant survival is shown in Table 5.18.

Table 5.18. Comparison of multivariable models for 2 year graft, patient and transplant survival

Graft survival model	Patient survival model	Transplant survival model
PVD	Heart failure	Heart failure
Obesity	Cerebrovascular disease	Cerebrovascular disease
	Chronic liver disease	
Recipient age	Recipient age	Recipient age*
Transplant type	Transplant type*	Transplant type*
Time on dialysis	Time on dialysis	Time on dialysis
Recipient ethnicity*	Primary renal disease	Primary renal disease
Highly sensitised		Highly sensitised
Donor age		Donor age
HLA MM level		

*p>0.05

A decision was made *a priori* to retain recipient age and transplant type in all models due to clinical significance and as such these factors were not necessarily statistically significant ($p<0.05$) in all models; where this is the case it is marked with an Asterix. Similarly, the ethnicity variable did not quite reach statistical significance ($p=0.089$) but was retained in the model due to clinical significance.

5.3.5. Sensitivity analyses

The same multivariable modelling techniques were employed to run a series of sensitivity analyses, in order to test the robustness of the results. Sub-cohorts of kidney only transplant recipients (n=2100), first transplant recipients (n=1946) and deceased donor transplant recipients (n=1438) were modelled using multivariable Cox regression for 2 year graft survival (Table 5.19), patient survival (Table 5.20) and transplant survival (Table 5.21). The results in all sub-cohorts were largely comparable to the models for the full study cohort.

Table 5.19. 2 year graft survival multivariable models for sub-cohorts

Variables	Kidney only recipients [n=2100]			First transplant recipients [n=1946]			Deceased donor recipients [n=1438]		
	HR	[95% CI]	p-value	HR	[95% CI]	p-value	HR	[95% CI]	p-value
Peripheral vascular disease	**2.66**	**[1.22, 5.80]**	**0.014**	**2.63**	**[1.12, 6.18]**	**0.026**	**3.09**	**[1.46, 6.52]**	**0.003**
BMI									
Underweight (<18.5)	1.71	[0.51, 5.69]	0.383	1.25	[0.29, 5.41]	0.764	0.82	[0.11, 6.17]	0.850
Normal (18.5 - 24.9)	1 [ref]			1 [ref]			1 [ref]		
Overweight (25.0 - 29.9)	1.50	[0.92, 2.45]	0.102	1.14	[0.66, 1.99]	0.639	1.48	[0.86, 2.56]	0.162
Obese (≥30.0)	**1.94**	**[1.15, 3.27]**	**0.013**	**1.83**	**[1.03, 3.23]**	**0.039**	**2.34**	**[1.34, 4.11]**	**0.003**
Recipient age (per 10 years)	0.84	[0.70, 1.00]	0.052	**0.81**	**[0.67, 0.99]**	**0.041**	0.84	[0.68, 1.03]	0.098
Recipient ethnicity									
White	1 [ref]			1 [ref]			1 [ref]		
Asian	0.74	[0.35, 1.54]	0.422	0.90	[0.42, 1.90]	0.773	0.84	[0.40, 1.78]	0.654
Black	1.71	[0.94, 3.11]	0.082	1.45	[0.73, 2.89]	0.288	1.55	[0.81, 2.98]	0.189
Other	0.50	[0.07, 3.62]	0.491	0.71	[0.10, 5.23]	0.737	0.61	[0.08, 4.40]	0.617
Time on dialysis									
Pre-emptive	1 [ref]			1 [ref]			1 [ref]		
0 - 3 years	1.18	[0.57, 2.45]	0.661	1.18	[0.57, 2.46]	0.663	1.73	[0.60, 4.98]	0.311
> 3 years	**2.12**	**[1.03, 4.36]**	**0.040**	**2.13**	**[1.01, 4.50]**	**0.046**	**2.94**	**[1.05, 8.27]**	**0.041**
Highly sensitised (cRF≥85%)	**2.27**	**[1.33, 3.85]**	**0.003**	0.62	[0.15, 2.56]	0.510	**2.10**	**[1.13, 3.90]**	**0.019**
Transplant type									
Living donor KO	1 [ref]			1 [ref]			.	.	.
Deceased donor KO	**1.93**	**[1.10, 3.37]**	**0.022**	**2.10**	**[1.08, 4.07]**	**0.029**	1 [ref]		
SPK	.	.	.	1.30	[0.35, 4.77]	0.696	0.47	[0.13, 1.70]	0.251
Donor age (per 10 years)	**1.23**	**[1.05, 1.42]**	**0.012**	**1.26**	**[1.05, 1.51]**	**0.013**	**1.26**	**[1.05, 1.51]**	**0.011**
HLA MM group									
1	1 [ref]			1 [ref]			1 [ref]		
2	**2.48**	**[1.06, 5.80]**	**0.037**	**4.33**	**[1.02, 18.42]**	**0.047**	**2.89**	**[1.07, 7.81]**	**0.036**
3	2.06	[0.91, 4.65]	0.084	2.86	[0.68, 11.95]	0.151	2.19	[0.83, 5.76]	0.113
4	1.64	[0.58, 4.61]	0.352	3.29	[0.72, 15.10]	0.126	3.12	[0.96, 10.10]	0.058

Table 5.20. 2 year patient survival multivariable models for sub-cohorts

Variables	Kidney only recipients [n=2100]			First transplant recipients [n=1946]			Deceased donor recipients [n=1438]		
	HR	[95% CI]	p-value	HR	[95% CI]	p-value	HR	[95% CI]	p-value
Heart failure	**3.45**	**[1.72, 6.90]**	**0.0005**	**4.05**	**[1.98, 8.26]**	**0.0001**	**3.43**	**[1.63, 7.21]**	**0.001**
Cerebrovascular disease	**2.72**	**[1.42, 5.23]**	**0.003**	2.01	[0.96, 4.22]	0.064	**3.14**	**[1.57, 6.29]**	**0.001**
Chronic liver disease	**4.22**	**[1.51, 11.77]**	**0.006**	**4.12**	**[1.45, 11.70]**	**0.008**	**5.14**	**[1.80, 14.67]**	**0.002**
Recipient age (per 10 years)	**1.77**	**[1.42, 2.22]**	**<0.0001**	**1.73**	**[1.06, 1.08]**	**<0.0001**	**1.67**	**[1.29, 2.16]**	**0.0001**
Primary renal disease									
Polycystic kidney disease	1 [ref]			1 [ref]			1 [ref]		
Diabetic nephropathy	**4.10**	**[1.47, 11.43]**	**0.006**	**3.77**	**[1.35, 10.64]**	**0.012**	2.74	[0.94, 7.96]	0.064
Glomerulonephritis	**2.81**	**[1.02, 7.72]**	**0.045**	**2.87**	**[1.02, 8.04]**	**0.045**	2.53	[0.90, 7.07]	0.077
Pyelonephritis	2.38	[0.72, 7.90]	0.156	2.08	[0.55, 7.83]	0.280	1.82	[0.48, 6.89]	0.377
Hypertensive nephropathy	**4.35**	**[1.37, 13.82]**	**0.013**	**4.29**	**[1.29, 14.21]**	**0.017**	**4.33**	**[1.36, 13.81]**	**0.013**
Renal vascular disease	3.30	[0.63, 17.20]	0.156	3.00	[0.58, 15.67]	0.193	3.36	[0.64, 17.57]	0.152
Other	**4.36**	**[1.57, 12.10]**	**0.005**	**3.79**	**[1.30, 11.01]**	**0.014**	2.12	[0.67, 6.75]	0.204
Uncertain	1.45	[0.42, 5.03]	0.156	1.46	[0.42, 5.06]	0.554	1.28	[0.37, 4.46]	0.699
Time on dialysis									
Pre-emptive	1 [ref]			1 [ref]			1 [ref]		
0 - 3 years	1.41	[0.55, 3.57]	0.475	0.86	[0.36, 2.05]	0.726	0.62	[0.23, 1.68]	0.350
> 3 years	**3.25**	**[1.34, 7.91]**	**0.009**	**2.97**	**[1.32, 6.70]**	**0.009**	1.96	[0.80, 4.77]	0.139
Transplant type									
Living donor KO	1 [ref]			1 [ref]			.	.	.
Deceased donor KO	1.08	[0.60, 1.96]	0.792	1.09	[0.55, 2.16]	0.801	1 [ref]		
SPK	.	.	.	.	.	.	1.79	[0.56, 5.77]	0.329

Table 5.21. 2 year transplant survival multivariable models for subcohorts

Variables	Kidney only recipients [n=2100]			First transplant recipients [n=1946]			Deceased donor recipients [n=1438]		
	HR	[95% CI]	p-value	HR	[95% CI]	p-value	HR	[95% CI]	p-value
Heart failure	**2.37**	**[1.38, 4.07]**	**0.002**	**3.17**	**[1.81, 5.54]**	**<0.0001**	**2.21**	**[1.20, 4.05]**	**0.011**
Cerebrovascular disease	**1.82**	**[1.10, 2.97]**	**0.018**	1.48	[0.85, 2.56]	0.166	**1.76**	**[1.04, 2.97]**	**0.035**
Recipient age (per 10 years)	1.10	[0.97, 1.26]	0.151	1.07	[0.93, 1.24]	0.345	1.07	[0.91, 1.26]	0.425
Primary renal disease									
Polycystic kidney disease	1 [ref]			1 [ref]			1 [ref]		
Diabetic nephropathy	**2.37**	**[1.26, 4.46]**	**0.007**	**2.47**	**[1.28, 4.80]**	**0.007**	1.96	[0.99, 3.88]	0.053
Glomerulonephritis	1.73	[0.97, 3.09]	0.065	**2.06**	**[1.11, 3.84]**	**0.023**	1.58	[0.84, 2.98]	0.160
Pyelonephritis	1.47	[0.74, 2.92]	0.273	1.40	[0.62, 3.16]	0.425	1.44	[0.67, 3.12]	0.352
Hypertensive nephropathy	**2.24**	**[1.09, 4.60]**	**0.028**	**2.42**	**[1.11, 5.24]**	**0.026**	2.09	[0.96, 4.52]	0.063
Renal vascular disease	2.11	[0.70, 6.32]	0.182	2.12	[0.70, 6.46]	0.186	2.23	[0.73, 6.79]	0.157
Other	**2.34**	**[1.28, 4.26]**	**0.006**	**2.43**	**[1.26, 4.66]**	**0.008**	1.68	[0.85, 3.34]	0.138
Uncertain	1.50	[0.76, 2.95]	0.243	1.48	[0.72, 3.08]	0.290	1.34	[0.65, 2.18]	0.429
Time on dialysis									
Pre-emptive	1 [ref]			1 [ref]			1 [ref]		
0 - 3 years	1.06	[0.63, 1.81]	0.819	0.96	[0.57, 1.62]	0.962	1.08	[0.53, 2.18]	0.838
> 3 years	**2.09**	**[1.25, 3.50]**	**0.005**	**2.21**	**[1.32, 3.69]**	**0.0003**	**2.28**	**[1.17, 4.45]**	**0.016**
Highly sensitised	**1.60**	**[1.06, 2.44]**	**0.027**	0.80	[0.33, 1.96]	0.625	1.41	[0.86, 2.32]	0.177
Donor age (per 10 years)	**1.13**	**[1.00, 1.27]**	**0.046**	**1.14**	**[1.01, 1.30]**	**0.047**	**1.20**	**[1.04, 1.37]**	**0.008**
Transplant type									
Living donor KO	1 [ref]			1 [ref]			.	.	.
Deceased donor KO	1.36	[0.93, 1.99]	0.115	1.29	[0.84, 1.99]	0.249	1 [ref]		
SPK	.	.	.	0.99	[0.39, 2.50]	0.987	0.94	[0.41, 2.17]	0.881

5.4. Discussion

In this national prospective cohort study, the key recipient comorbid conditions that predict poorer survival outcomes within two years after kidney transplantation have been identified. PVD and obesity were associated with a two- to three- fold increased risk of graft failure within two years of transplantation. Different comorbidities impacted on patient survival, and the risk of death within two years of transplantation was approximately doubled for CVD, tripled for heart failure and quadrupled for CLD. With comprehensive adjustment for comorbidity and case-mix in this national analysis, it was also possible to demonstrate no differences in survival outcomes between the 23 transplant centres in the UK.

As well as analysing graft and patient survival separately, we also investigated a combined transplant survival outcome defined as the earliest of graft failure or patient death. This definition of transplant survival which incorporates death with a functioning graft is often used in the transplant literature as it demonstrates the overall success of the transplant.[183, 185] However, we found that this method failed to demonstrate the importance of several comorbidity risk factors that were significant for graft survival (PVD, obesity) and patient survival (CLD) separately. This is because the comorbidities affecting graft and patient survival are different, therefore their effects are blunted when analysing the composite end-point of transplant survival. This was also apparent when considering confounding factors, where the effects of several factors which influenced graft survival but not patient survival (recipient ethnicity, transplant type, HLA MM level) were lost in the transplant survival

model. A further problematic scenario was encountered with recipient age. We found that while recipient age significantly increased the risk of patient death, it actually reduced the risk of graft failure - a finding that is well documented throughout the literature and is due to the decreased immunocompetence of older age.[186-188] Thus, the opposite effects of age on graft and patient survival caused the effects to be essentially cancelled out in the transplant survival analysis. This demonstrates the importance of distinguishing between graft and patient survival when investigating factors which impact on survival outcomes after kidney transplantation.

Graft survival rates for kidney transplantation have progressively improved over time, largely due to advances in immunosuppressive therapies leading to a reduction in the rate of rejection.[13] Our results confirmed excellent overall 2 year graft survival rates of 94.8%, which is in keeping with national UK transplant registry data for the period of the study.[13] Previous research has focussed on the influence of immunological, donor and transplant related factors on graft survival,[61, 184, 189] however the impact of recipient factors such as comorbidity on the risk of graft failure have not been widely studied.

In this study, a history of PVD at the time of transplantation was found to significantly increase the risk of graft failure by a factor of 2.77, after adjustment for confounding factors. PVD is typically diagnosed clinically by measuring the ankle-brachial pressure index (ABPI), and our results are in agreement with a US study of 819 patients which reported a 2.77 fold increase in the risk of graft failure for patients with a low ABPI (<0.9).[190] Previous studies have reported inferior transplant survival (uncensored for death)

among PVD patients, largely due to death from cardiovascular causes.[191-193] Our results contradict these findings, as we found PVD to be a risk factor for death censored graft survival and not for patient survival or transplant survival, after adjustment for other factors. However, these studies were performed in earlier US patient cohorts. Improved management of cardiovascular risk factors among the PVD patients in our more contemporary UK cohort may explain why PVD patients were not at increased risk of death in our study, and instead survived to demonstrate the intrinsic negative effect of PVD on the graft. We were unable to confirm the mechanism of graft loss among the patients with PVD in our study. However, there are a number of means by which PVD may impact the success of a kidney transplant. Pre-existing PVD of the aorta or iliac arteries may complicate the positioning of the kidney graft, resulting in difficult anastomoses, cholesterol emboli or hypoperfusion of the graft, and subsequent failure in the early post-operative period.[194, 195] In the longer term, *de novo* atherosclerotic lesions of the transplant renal artery or proximal iliac artery can lead to transplant renal artery stenosis, which if not recognised and treated promptly can have devastating consequences including graft loss, refractory hypertension, pulmonary oedema and ultimately patient death.[196, 197] The majority of graft failures among PVD patients in our study were early (within the first 30 days post-transplantation), thus implying that graft loss was related to pre-existing rather than *de novo* PVD. Patients with ESRD are at increased risk of developing PVD, as renal impairment is a significant risk factor for the disease.[198] However, the impact of transplantation on the progression of pre-existing PVD is not clear. There is some evidence that transplantation may reduce the incidence of *de novo* PVD, when compared with patients remaining

on the transplant waiting list.[199] On the other hand, transplant recipients are exposed to immunosuppressive drugs in the post-operative period which often lead to hyperglycaemia, hypertension and hyperlipidaemia; all of which are potent atherogenic factors which may lead to the development or exacerbation of PVD.[200-202] Despite being a high risk group, patients with PVD still derive a significant survival benefit from transplantation over dialysis.[203-205] As such PVD should not preclude transplantation, but efforts should focus on minimising cardiovascular risk factors, careful pre-operative planning, maintaining a high index of suspicion to enable early detection of complications in the graft and fully informed discussion with patients about the increased risks of graft loss.

Obesity is a major public health issue.[206] It was the most prevalent comorbidity among the patients in this study, with 20.6% patients obese at the time of transplantation. Obesity is an ongoing topic of controversy with regard to patient suitability for kidney transplantation. Some centres do not exclude patients with obesity from transplantation, while others restrict access to the waiting list on the basis of specific BMI thresholds, which may differ considerably between centres, and even between clinicians within the same centre.[6] This variability is not surprising given that current best practice guidelines do not offer clear advice on the topic. UK Renal Association guidelines suggest that obesity (BMI >30 kg/m^2) is not an absolute contraindication to transplantation, but that patients be screened rigorously for cardiovascular disease, each case considered individually, and individuals with a BMI >40 kg/m^2 are less likely to benefit.[125] The Kidney Health Australia - Caring for Australasians with Renal Impairment (KHA-CARI) guidelines give

similar recommendations.[207] European renal best practice guidelines state that patients with a BMI >30 kg/m^2 should reduce weight before transplantation.[208] Canadian society of transplantation guidelines recommend supervised weight-loss for obese candidates, with target BMI < 30 kg/m^2 but state that whether a patient should be denied kidney transplantation solely on the basis of obesity is a matter of debate.[209] American guidelines do not offer specific recommendations on obesity, and advise clinicians to refer to their specific centre policy.[210, 211] Although early single centre studies failed to show any impact of obesity on graft survival,[55, 212, 213] more recent multicentre analyses and systematic reviews have confirmed that obesity does significantly reduce graft survival.[53, 214-217] Our results are in keeping with this evidence as we found that obesity conferred a 1.96 fold increase in the risk of graft loss within 2 years. Obesity is a strong risk factor for the development of chronic kidney disease (CKD) and ESRD,[218] and there is growing evidence for the mechanisms by which obesity leads to a decline in renal function in native kidneys. Obesity induces glomerular hyperfiltration, hypertension, proteinuria, glomerulomegaly and glomerulosclerosis, resulting in progressive renal impairment.[219-221] As well as changing renal haemodynamics, excess adipose tissue produces adipokines that promote inflammation and glomerular injury.[222] Lipid accumulation in the kidney causing essentially a “fatty kidney” also increases insulin resistance and further mediates glomerular damage via cell dysfunction.[223] It is not yet clear whether these same mechanisms could explain the deleterious effect of obesity on transplanted kidneys. The fact that the greater risk of graft loss for obese patients in our study was not apparent until over a year post-transplantation, may support the theory of a progressive pathological process. A study of 838 transplant recipients found

that at 1 year post-transplant, higher BMI was associated with hyperfiltration in the graft, which in turn was associated with graft loss.[224] Another possible explanation for inferior graft survival among obese transplant recipients, is difficulties in achieving and maintaining the narrow therapeutic target concentrations of immunosuppressive drugs.[225] For obese CKD patients (not receiving renal replacement therapy), there is some evidence that weight loss significantly reduces proteinuria and may halt the progression of renal impairment.[226, 227] However, these findings have not been able to be reproduced among patients undergoing transplantation. A large registry analysis of kidney transplant recipients in the US found no benefit for pre-transplant weight loss on graft or patient survival.[228] Although, the study was limited by the inability to determine whether weight loss was intentional or the result of declining clinical condition. The latter would of course confound survival results. While we found that obesity was a risk factor for graft loss, we did not find any significant effect for obesity on patient survival. This is consistent with the results of a recent systematic review and meta-analysis including 17 studies and 138,081 patients.[215] This finding may be related to the well-recognised obesity paradox in patients undergoing maintenance dialysis, whereby increasing BMI is paradoxically associated with decreasing mortality risk.[229, 230] It is possible that obese patients on dialysis are in a better clinical and nutritional state at the point of transplantation compared with their non-obese counterparts,[231] allowing them to cope better with the stresses of transplantation. Hence, this may offset any negative association of obesity on patient survival after transplantation. Despite the obesity paradox of dialysis, obese patients still derive a significant survival benefit from transplantation.[54, 232, 233] A registry study in the UK showed a clear survival

benefit for patients undergoing transplantation over those who remained on the waiting list across all BMI bands, with a fivefold increase in survival for transplanted patients.[233] As well as being at higher risk of graft loss, obese patients are also known to have higher rates of delayed graft function (DGF), surgical site infection, wound dehiscence and incisional hernia following transplantation.[216, 234, 235] Obesity is a potentially reversible condition. However, with worse outcomes after transplantation but better outcomes on dialysis, there are complex and controversial questions surrounding the optimal management of obese patients with ESRD. The results of the present study can be used to carefully counsel patients with obesity about the increased risks of graft loss. Further prospective studies are required to assess whether pre-transplant weight loss can improve outcomes.

Patients with ESRD have a significantly elevated risk of cardiovascular disease compared with the general population.[171, 236] Although this risk is somewhat alleviated by transplantation, cardiovascular events remain the leading cause of post-transplant mortality.[237] Thus, it was not unexpected that a number of cardiovascular comorbidities were found to be significant risk factors for patient death in the present study. Nevertheless, identifying and quantifying these risks is vital for evidence-based decision making and patient counselling. Heart failure led to a 3.37 increased risk of mortality within 2 years after kidney transplantation in the study. With the acknowledgement that it can be difficult to make a clear distinction between heart failure and fluid overload in patients on dialysis; the findings demonstrate that a diagnosis of heart failure in the patient's record predicts poorer survival, irrespective of how the diagnosis was made or the exact pathophysiology. It

is noteworthy that despite the significant detrimental effect of heart failure on post-transplant survival, no effect was observed for ischaemic heart disease. Cardiac risk factors are often pooled together in observational studies, with a tendency to think of cardiac disease as denoting ischaemic atherosclerotic disease only.[238] This study is one of very few to examine the distinct diagnoses separately. The findings support the results of a single centre study which found that patients with pre-existing impaired left ventricular systolic function were at significantly higher risk of both cardiac mortality and all-cause mortality after transplantation, while cardiac ischaemia was not.[239] These results mirror the finding that among dialysis patients, heart failure is a more potent predictor of death than ischaemic heart disease.[240] They could also signify that the current risk stratification of patients with ischaemic heart disease in the context of renal transplantation in the UK is effective. Previous research has shown that kidney transplantation can improve the morphological and functional abnormalities of heart failure.[241, 242] However, such improvement is impeded by a longer duration on dialysis pre-transplantation.[242, 243] It is thought that this is the result of a more prolonged exposure to uraemic toxins that are detrimental to myocardial contractility.[238, 244] This would suggest that patients with heart failure would benefit from minimising time spent on dialysis and pursuing early transplantation. Given the current deceased donor shortage and length of the waiting list, it is likely that living donor kidney transplantation would provide the best option for these patients.

CVD was identified as another significant risk factor for mortality, conferring a 2.51 elevated risk of death within 2 years post-transplantation. It is known

that patients with ESRD and kidney transplant recipients have more severe carotid atherosclerosis than the general population and are at substantially greater risk of stroke.[245-248] A large US registry analysis demonstrated that transplantation reduced the risk of cerebrovascular events from 11.8% to 6.8% compared to patients remaining on the waiting list.[249] However, previous CVD remains a strong risk factor for further post-transplantation events and mortality.[247, 250, 251] Post-transplantation cerebrovascular events are associated with high mortality,[252] which is worse for haemorrhagic strokes (48%) compared with ischaemic strokes (6%).[251] In a prospective randomised controlled trial including 1652 kidney transplant recipients (ALERT trial), the use of Fluvastatin did not reduce the incidence cerebrovascular events or mortality.[251] Further trials are needed to assess the ability of therapies to reduce the risk of further cerebrovascular events and mortality in this high risk population.

CLD was associated with a 3.97 times greater risk of mortality in this study. There is a paucity of published research regarding CLD and kidney transplant outcomes. Previous studies have focussed on the role of hepatitis B and C related liver disease as predictors of increased mortality after kidney transplantation.[253-255] To our knowledge, this is the first study to demonstrate that CLD of any aetiology leads to reduced survival after kidney transplantation. Further research is required to understand the underlying mechanisms. A national survey of transplant surgeons demonstrated substantial heterogeneity of opinion and current practices with regards to the management of patients with compensated liver cirrhosis and ESRD.[256] The majority of respondents (69.5%) stated they would consider these patients for

renal transplantation alone, 26.9% believed they could only be considered for simultaneous liver-kidney transplantation, and 3.6% believed that this population of patients were not suitable for kidney transplantation. The results of our study can be used to quantify the risks of kidney transplantation in patients with CLD in order to aid decision making and discussion with patients.

Diabetes has long been recognised as a risk factor for mortality after transplantation, primarily due to elevated cardiovascular risk.[257] The survival advantage of renal transplantation over dialysis for diabetic patients is also well documented.[7, 8, 258] However, more recently several studies have shown a decrease in the post-transplant mortality of diabetic patients over time, resulting in a narrowing of the mortality difference between diabetics and non-diabetics to the point of largely eliminating it.[259, 260] This has been attributed to enhanced management of glycaemic control, increased use of cardioprotective medications and improvement in post-operative care. This may explain the finding in our study that having a diagnosis of diabetes was only associated with inferior patient survival after transplantation if diabetes was the cause of renal failure, and that there was no survival disadvantage for patients with uncomplicated diabetes.

Pre-transplant time on dialysis is a well-recognised risk factor for inferior graft and patient survival after transplantation.[20] Compared with kidney transplantation, dialysis is a less effective renal replacement therapy and results in the accumulation of uraemia-related risk factors such as inflammation, oxidative stress, malnutrition and hyperhomocysteinaemia,

leading to increased cardiovascular risk.[261] In a paired donor kidney analysis in the US, Meier-Kriesche et al. demonstrated that the detrimental dose effect of dialysis on graft loss and patient death after transplantation was evident even after just 6 months on dialysis.[19] This was confirmed in subsequent US studies.[262, 263] In our study, dialysis was only associated with inferior graft and patient survival after a period of 3 years. It is known that mortality on dialysis is significantly higher in the US than in the UK,[114, 264] and this may explain some of the difference between our results and those of the US studies. Furthermore, improvements in dialysis care and outcomes over time may account for the reduced effect of dialysis on survival in our more contemporary cohort.[265] This is supported by more recent analyses in European cohorts showing a reduction in the influence of dialysis vintage on transplantation outcomes in the current era.[266, 267]

It is long established that living donor kidney transplants provide superior survival outcomes compared to deceased donor kidney transplants.[18, 122] Despite this, there are few studies comparing outcomes of living and deceased donor kidney transplant outcomes with adjustment for comorbidity. In the present analysis we were able to account for significant comorbidity variables in a fully adjusted multivariable model. This demonstrated that 2 year graft survival was significantly better for living donor versus deceased donor transplantation, however no significant differences in patient survival were found. Of note, in the graft survival model, the addition of the CIT variable caused the transplant type variable to lose significance, indicating that the difference in graft survival between living and deceased donor transplants can largely be explained by the difference in

CIT. The lack of difference in patient survival suggests that recipient variables including comorbidity may be more important for patient survival outcomes within 2 years than the type of donor. These findings are in keeping with a study which assessed the ability of a number of comorbidity indices in predicting mortality after kidney transplantation in a cohort of UK transplant recipients.[268] In all multivariable models, comorbidity score and age were significant, while donor type was not.

An important outcome of this study was that we did not find any evidence of inter-centre variation in survival outcomes between the 23 UK transplant centres. Reports from the UK Transplant Registry have identified several centres in the UK with graft and patient survival rates lower than the national rate,[269] however, these registry analyses are not adjusted for recipient comorbidity. Thus, our results would suggest that any centre disparities in survival outcomes are due to variations in patient case-mix and comorbidity and provide a strong argument for including prospectively collected comorbidity data in future registry analyses. Our findings are in keeping with a previous study of patients on renal replacement therapy (including dialysis and transplant patients) in England, where nearly all variation in survival between centres was explained by demographic and comorbidity variables obtained by linkage to the Hospital Episode Statistics database.[270] In contrast, studies in the US and Canada have demonstrated persistent centre differences in survival outcomes after transplantation despite adjustment for recipient comorbidity and other prognostic factors.[169, 271]

A major strength of the present study is that it is a prospective and comprehensive analysis of a large cohort of transplant recipients from all UK transplant centres. There are a number of limitations. We used relatively broad definitions for each comorbidity and were unable to distinguish between differing levels of severity or duration for each condition. All comorbidity data were collected at the time of transplantation when patients were recruited to the study. Therefore, we were unable to assess the progression or improvement of each condition after transplantation, and whether this impacted on outcomes. These limitations were compromises that allowed us to prospectively collect data on a wide range of comorbid conditions in a national cohort of transplant recipients. As it was not possible to recruit the entire kidney transplant population, the study is at risk of selection bias. It is reassuring that the distribution of age, gender and type of transplant is similar in the study population versus the national kidney transplant population. However, the study did include a significantly higher proportion of White patients compared with the national kidney transplant population. Therefore, the conclusions within this analysis are less certain for patients from Black, Asian and other ethnic backgrounds. Finally, the results from this observational study describe associations only and no causation can be inferred.

The increasing prevalence of comorbidities in the ESRD population poses a significant challenge for the assessment of patient suitability for kidney transplantation as well as predicting the risks and outcomes of individual patients. This study identifies several comorbidities that negatively impact on 2 year graft and patient survival after kidney transplantation. Obesity and

PVD compromise graft survival, while heart failure, CVD and CLD increase patient mortality. Interestingly, the identified comorbidities share common risk factors that link them all to the so called metabolic syndrome. This global epidemic is estimated to affect around a quarter of the world's population, and prevalence is increasing rapidly. Together with the ageing population, this will lead to growing numbers of high risk patients being referred for transplantation. The risk-benefit ratio of transplantation should be carefully considered in these populations. With the recent landmark Montgomery case,[272] awareness and communication of risks to patients are increasingly important. Our study provides up to date evidence that can be used during the informed consent process, to correctly portray the risks conferred by specific comorbidities on kidney transplantation. Further research is needed to determine whether optimisation of these comorbid conditions can improve graft and patient survival. Needless to say, prevention is better than cure, and there should be increased efforts to address risk factors early in order to prevent the development and progression of comorbidity among patients with ESRD.

CHAPTER 6

Patient Reported Outcome Measures of Living Donor and Deceased Donor Kidney Transplantation

6.1. Introduction

Clinicians have a limited understanding of the impact a health condition or treatment may have on patients' daily lives.[273] For this reason, patient reported outcome measures (PROMS) are increasingly recognised as important indicators in healthcare. PROMS allow patients to express their assessment of their health and quality of life (QoL). PROMS is an umbrella term that encompasses a wide variety of different outcomes including health status, well-being, QoL and treatment satisfaction. The most widely used instruments are those that measure patient reported health status, otherwise known as health-related quality of life (HRQoL). PROMS may also be general or condition-specific. While general PROMS are applicable for any condition and allow comparison between different patient populations or with the general population, condition-specific instruments are increasingly used to provide more detailed information about patients' experiences in the context of a particular health condition.[274, 275]

With continued improvements in the life expectancy after kidney transplantation, quality of life is an increasingly important issue for kidney transplant recipients. Despite this, PROMS research in this population is limited. Most studies have focussed on HRQoL in kidney transplant recipients relative to patients on dialysis, and several meta-analyses have shown results in favour of kidney transplantation.[63, 103, 276] However, HRQoL only measures patients' perceived general health status, and there is lack of data for other non-health related aspects of life (e.g. wellbeing) as well as domains which are specific to having a renal condition (e.g. dietary restrictions). Furthermore,

while it is widely acknowledged that living donor kidney transplantation (LDKT) provides superior survival outcomes compared with deceased donor kidney transplantation (DDKT), very few studies have explored whether any differences in PROMS exist between the two recipient groups. It is known that transplantation results in considerable psychological implications for transplant recipients and that appropriate support is important to aid adjustment and avoid issues which may undermine the success of the transplant. However, the needs of LDKT and DDKT recipients may differ considerably.[277] In DDKT, the recipient's transplant depends on the death of another human being, while in the case of LDKT, donors are usually close family members who undergo a major operation with its own risks. Each of these scenarios may lead to distinct psychosocial issues and consequences on the recipient's quality of life.[278]

This aim of this analysis was to compare a range of PROMS in LDKT and DDKT recipients 1 year post-transplantation, adjusting for relevant sociodemographic and clinical factors.

6.2. Methods

6.2.1. Study population

A subset of 262 kidney-only transplant recipients from the ATTOM incident transplant cohort (n=2262) were invited to complete PROMS questionnaires at 1 year post-transplantation. The subset was recruited in a quasi-random manner (the first patient to be recruited to the incident transplant cohort each month in each transplant centre). In each centre, recruitment took place over a 12-month period, between 1st November 2011 and 31st March 2013 and patients aged 18 – 75 years were eligible for recruitment. The subset included both LDKT (n=118) and DDKT (n=144) recipients. For the purposes of this analysis, multi-organ transplant recipients were excluded. A total of 214 (81.7%) patients responded and returned the questionnaires (Figure 6.1), all of whom had a functioning graft at 1 year.

6.2.2. Data variables

The primary outcome measures were patients' self-reported health status, well-being, general quality of life, renal-dependent quality of life and treatment satisfaction. These measures were assessed by the following questionnaires (Table 6.1); EuroQol five dimensions (EQ-5D) including the EuroQol visual analogue scale (VAS),[279] the 12-item well-being questionnaire (W-BQ12),[280, 281] renal-dependent quality of life (RDQoL) which includes a general quality of life measure,[282] renal treatment satisfaction (RTSQs)[283] and renal treatment satisfaction change version (RTSQc)[283]. Questionnaires were either posted to patients or were completed online, and were provided in other languages if required.

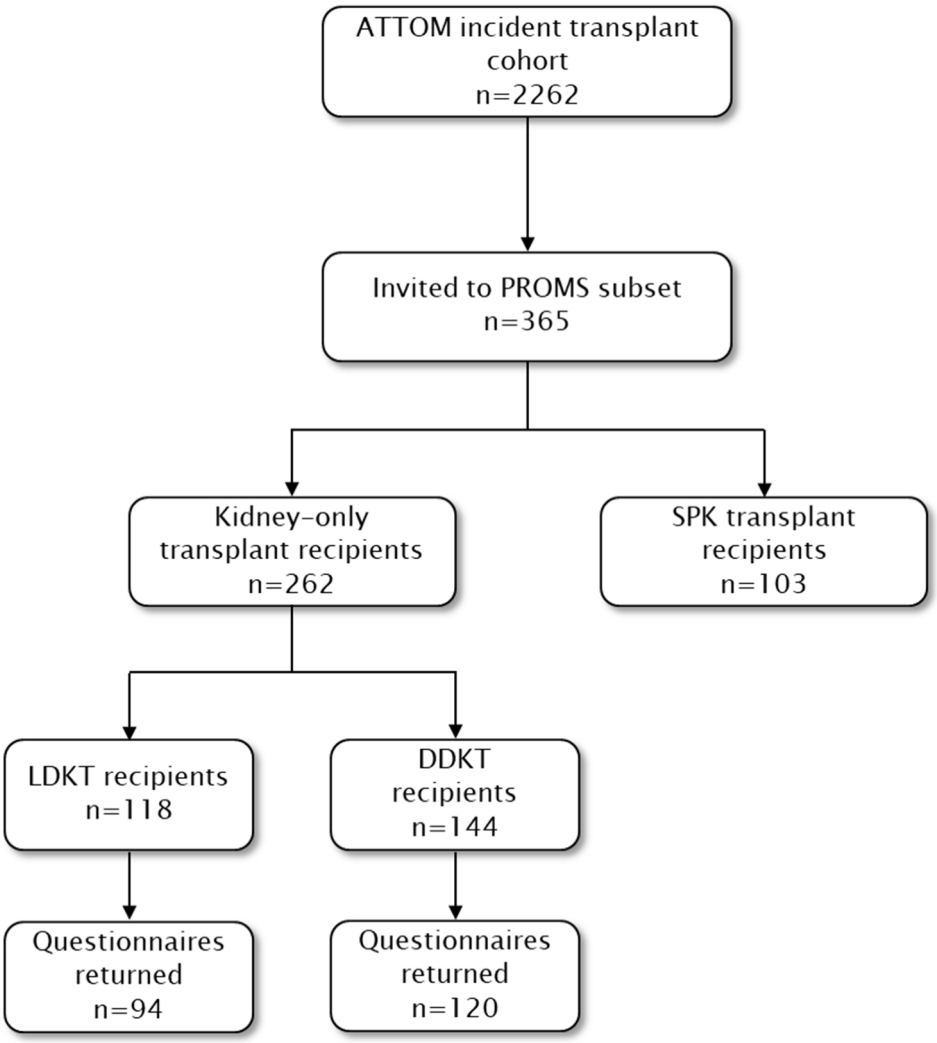

Figure 6.1. Study population

Table 6.1. PROMS questionnaires

Questionnaire	Description	Range of possible scores

EuroQol five dimensions (EQ-5D)	• General health status
	• 5 dimensions of health (today):
	  ○ Mobility
	  ○ Self-care
	  ○ Usual activities
	  ○ Pain / Discomfort
	  ○ Anxiety / Depression
	• Rated on 5 levels
	  ○ No problems
	  ○ Slight problems
	  ○ Moderate problems
	  ○ Severe problems
		-0.281 to +1.00

	○ Extreme problems • Converted to weighted index score using the value set for England[275] • Higher score indicates better health status	
EuroQol visual analogue scale (VAS)	• General health status • Rating of health (today) on visual analogue scale • 0 = worst health you can imagine • 100 = best health you can imagine	0 to 100
12-Item Well-Being Questionnaire (W-BQ12)	• General well-being • Calculated by combining scores from 3 subscales (12 items) ○ Negative well-being ○ Energy ○ Positive well-being • Higher score indicates greater well-being	0 to 36
General QoL (from RDQoL questionnaire)	• General QoL • Single item question rated from -3 (extremely bad) to +3 (excellent)	-3 to +3
Renal-dependent QoL (RDQoL)	• 17 aspects of life • Rating of impact of renal condition • Rating of importance of each aspect of life • Combined to give an average weighted impact score • From -9 (most negative impact) to +3 (most positive impact)	-9 to +3
Renal treatment satisfaction questionnaire status version (RTSQs)	• Satisfaction with current renal treatment • Rated from 6 (very satisfied) to 0 (very dissatisfied) on 13 items • Higher score indicates greater satisfaction	0 to 78
Renal treatment satisfaction questionnaire change version (RTSQc)	• Satisfaction with current renal treatment compared with satisfaction with previous renal treatment • Rated from +3 (much more satisfied now) to -3 (much less satisfied now) on 13 items • Higher score indicates greater satisfaction with current compared with previous treatment	-39 to +39

Baseline demographic, socioeconomic and clinical variables were collected at the time of transplantation (Appendix A.2). Variables of interest included:

(a) demographic variables: age, gender, ethnicity

(b) socioeconomic variables: civil status, highest qualification, employment status, car ownership, home ownership, health literacy

(c) clinical variables: transplant type, primary renal disease, modified Charlson Comorbidity Index (CCI), mental illness, body mass index (BMI), smoking status, previous transplantation, pre-emptive transplantation

Variable definitions are given in Appendix A.3. A modified Charlson Comorbidity Index (CCI) designed specifically for patients with ESRD was calculated for each patient using the methods described in Chapter 2. In order to reduce the number of degrees of freedom, the modified CCI was used during modelling rather than considering each comorbidity variable separately. The modified CCI was divided into 4 groups; 0, 1, 2 and ≥3. Mental illness was included separately as this is not part of the modified CCI score, but was hypothesised to be an important variable when analysing PROMS. BMI was grouped in accordance with the World Health Organisation (WHO) BMI classifications of Underweight (<18.5 kg/m^2), Normal (18.5 - 24.9 kg/m^2), Overweight (25.0 - 29.9 kg/m^2) and Obese (≥30.0 kg/m^2).[126]

6.2.3. Statistical methods

Baseline characteristics of LDKT and DDKT recipients were presented as numbers with percentages (%) and compared by chi-squared tests for categorical data. The effect of the type of transplant received (LDKT vs DDKT) on PROMS was analysed using generalised linear regression models adjusted

for all demographic, socioeconomic and clinical variables. The proportion of missing data is shown in Table 6.2. In the PROMS subset, data could not be assumed to be missing at random, and as such it was not appropriate to undertake multiple imputation. Therefore, patients with missing data were excluded and complete case analysis was performed. All data were analysed using SAS®9.4 (SAS Institute Inc, Cary, USA).

Table 6.2. Missing data

Variable	n [%]
Age	0 [0]
Gender	0 [0]
Ethnicity	0 [0]
Civil status	4 [1.9]
Qualifications	4 [1.9]
Employment status	4 [1.9]
Car ownership	4 [1.9]
Home ownership	4 [1.9]
Health Literacy	4 [1.9]
Primary renal disease	0 [0]
Modified CCI	0 [0]
Mental illness	0 [0]
BMI	18 [8.4]
Smoking status	28 [13.1]
Previous transplant	1 [0.5]
Pre-emptive transplant	0 [0]
EQ-5D	5 [2.3]
EQ-5D VAS	2 [0.9]
WBQ12	1 [0.5]
QoL	0 [0]
RDQoL	0 [0]
RTSQs	1 [0.5]
RTSQc	8 [3.7]

6.3. Results

6.3.1. Study population characteristics

A comparison of baseline characteristics between LDKT and DDKT recipients in the PROMS subset is displayed in Table 6.3. Compared to DDKT recipients, a significantly higher proportion of LDKT recipients were younger, married or living with a partner, had obtained qualifications, were employed, were car and home owners, had normal health literacy, had mental illness and underwent pre-emptive transplantation.

Table 6.3. Patient characteristics

Variable	DDKT n=120	LDKT n=94	p-value
Age group			0.005
18 – 34	12 [10.0]	22 [23.4]	
35 – 49	35 [29.2]	34 [36.2]	
50 – 64	50 [41.7]	31 [33.0]	
65 – 75	23 [19.2]	7 [7.5]	
Gender			0.532
Male	79 [65.8]	58 [61.7]	
Female	41 [34.2]	36 [38.3]	
Ethnicity			0.073
White	100 [83.3]	89 [94.7]	
Asian	10 [8.3]	3 [3.2]	
Black	8 [6.7]	2 [2.1]	
Other	2 [1.7]	0 [0]	
Civil status			0.034
Married / Living with partner	65 [55.6]	61 [65.6]	
Divorced / Separated / Widowed	29 [24.8]	10 [10.8]	
Single	23 [19.7]	22 [23.7]	
Qualifications			0.004
Higher education level	35 [29.9]	29 [31.2]	
Secondary education level	63 [53.9]	59 [63.4]	
No qualifications	19 [16.2]	5 [5.4]	
Employment status			0.032
Employed	45 [38.5]	48 [51.6]	
Unemployed	6 [5.1]	4 [4.3]	
Long term sick / disability	29 [24.8]	21 [22.6]	
Retired	32 [27.4]	11 [11.8]	

Other	5 [4.3]	9 [9.7]	
Car ownership	101 [86.3]	89 [95.7]	0.022
Home ownership	71 [60.7]	69 [74.2]	0.039
Health literacy			0.049
Normal	105 [89.7]	90 [96.8]	
Limited	12 [10.3]	3 [3.2]	
Primary renal disease			0.069
Diabetic nephropathy	11 [9.2]	3 [3.2]	
Glomerulonephritis	29 [24.2]	36 [38.3]	
Polycystic kidney disease	24 [20.0]	13 [13.8]	
Pyelonephritis	12 [10.0]	15 [16.0]	
Hypertensive nephropathy	7 [5.8]	2 [2.1]	
Renal vascular disease	3 [2.5]	0 [0]	
Other	21 [17.5]	16 [17]	
Uncertain	13 [10.8]	9 [9.6]	
Modified CCI			0.534
0	93 [77.5]	78 [83.0]	
1	10 [8.3]	8 [8.5]	
2	10 [8.3]	6 [6.4]	
≥3	7 [5.8]	2 [2.1]	
Mental illness	2 [1.7]	7 [7.5]	0.037
BMI (kg/m^2)			0.873
<18.5 (underweight)	3 [2.8]	2 [2.3]	
18.5 – 24.9 (normal)	40 [36.7]	37 [42.5]	
25.0 – 29.9 (overweight)	45 [41.3]	33 [37.9]	
>=30 (obese)	21 [19.3]	15 [17.2]	
Smoking status			0.353
Non-smoker	68 [66.0]	48 [57.8]	
Smoker	9 [8.7]	6 [7.2]	
Ex-smoker	26 [25.2]	29 [34.9]	
Previous transplant	15 [12.6]	15 [16.0]	0.485
Pre-emptive transplantation	14 [11.7]	38 [40.4]	<0.0001

Data are number [%]. P-values are for chi-squared test.
Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Table 6.2.

6.3.2. PROMS of LDKT vs DDKT

Median values for each PROMs outcome is shown for DDKT and LDKT recipients in Table 6.4. Univariable differences in PROMS between LDKT and DDKT recipients are shown in Table 6.5 with their 95% confidence intervals (95% CI). Compared to DDKT recipients, LDKT recipients had significantly higher scores for the EQ-5D VAS, general QoL, RDQoL and RTSQs (e.g. for

LDKT recipients the predicted EQ-5D VAS score was 4.51 units higher than for DDKT recipients, p=0.040).

Table 6.4. Median values for PROMS

Variable		DDKT		LDKT	
	Range	**n**	**Median (IQR)**	**n**	**Median (IQR)**
EQ-5D Utility	-0.281 to +1.00	117	0.90 (0.79-1.00)	92	0.94 (0.83-1.00)
EQ-5D VAS	0-100	119	80 (70-90)	93	85 (80-90)
WBQ12	0-36	120	27 (21-30.5)	93	28 (24-32)
General QoL	-3 to +3	120	1 (1-2)	94	2 (1-2)
RDQoL	-9 to +3	120	-2.19 (-4.09--1.12)	94	-1.52 (-2.77--0.56)
RTSQs	0-78	120	70.5 (64-77)	93	74 (68-77)
RTSQc	-39 to +39	113	33 (27-39)	93	35 (27-38)

Table 6.5. Univariable association of transplant type with PROMS

PROMS	Parameter estimate LDKT vs DDKT (ref)	95% CI	p-value
EQ-5D Utility	0.04	[-0.11, 0.09]	0.121
EQ-5D VAS	**4.51**	**[0.20, 8.82]**	**0.040**
WBQ12	1.40	[-0.45, 3.26]	0.138
General QoL	**0.42**	**[0.14, 0.69]**	**0.003**
RDQoL	**0.77**	**[0.25, 1.30]**	**0.004**
RTSQs	**3.51**	**[1.01, 6.01]**	**0.006**
RTSQc	0.05	[-3.23, 3.14]	0.975

Multivariable generalised linear regression models were created for each of the PROMS outcomes. Each model included transplant type as the variable of interest and was adjusted for recipient age, gender, ethnicity, civil status, qualifications, employment status, car ownership, home ownership, health

literacy, primary renal disease, modified CCI, mental illness, BMI, smoking status, previous transplantation and pre-emptive transplantation.

There was no significant difference in EQ-5D utility scores between LDKT and DDKT recipients in the adjusted multivariable model (parameter estimate 0.04, 95% CI -0.02, 0.10, p=0.231) (Table 6.6). The model showed that significantly higher EQ-5D utility scores were reported by single patients (compared with married patients or patients living with a partner) and patients with a primary renal disease of glomerulonephritis, polycystic kidney disease or pyelonephritis (compared with diabetic nephropathy as a primary renal disease). Unemployed patients and those on long term sick leave or off work due to disability reported significantly lower EQ-5D utility scores compared with employed patients.

Table 6.6. Multivariable analysis of factors associated with EQ-5D utility				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	0.04	-0.02	0.10	0.231
Age group				
18 – 34	[REF]			
35 – 49	0.01	-0.09	0.10	0.886
50 – 64	0.04	-0.07	0.14	0.486
65 – 75	0.04	-0.09	0.18	0.544
Gender				
Male	[REF]			
Female	-0.04	-0.09	0.02	0.236
Ethnicity				
White	[REF]			
Asian	-0.10	-0.20	0.003	0.058
Black	0.07	-0.07	0.20	0.340
Other	0.02	-0.22	0.25	0.885
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	0.04	-0.04	0.12	0.286
Single	0.13	0.04	0.22	0.005
Qualifications				
Higher education level	[REF]			
Secondary education level	0.01	-0.06	0.07	0.862
No qualifications	0.06	-0.04	0.17	0.244
Employment status				
Employed	[REF]			
Unemployed	-0.18	-0.33	-0.02	0.025
Long term sick / disability	-0.12	-0.19	-0.04	0.004
Retired	0.01	-0.08	0.10	0.832
Other	0.004	-0.10	0.11	0.943
Car ownership				
Yes	[REF]			
No	0.05	-0.06	0.15	0.375
Home ownership				
Yes	[REF]			
No	-0.02	-0.10	0.05	0.570
Health literacy				
Normal	[REF]			
Limited	-0.08	-0.21	0.05	0.221
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	0.22	0.08	0.36	0.002
Polycystic kidney disease	0.23	0.09	0.37	0.001
Pyelonephritis	0.25	0.10	0.40	0.001

Hypertensive nephropathy	0.16	−0.01	0.33	0.072
Renal vascular disease	−0.05	−0.32	0.22	0.717
Other	0.23	0.09	0.37	0.001
Uncertain	0.09	−0.07	0.24	0.262
Modified CCI				
0	[REF]			
1	0.10	−0.01	0.20	0.076
2	−0.01	−0.11	0.09	0.795
≥3	−0.06	−0.21	0.08	0.406
Mental illness				
No	[REF]			
Yes	−0.10	−0.22	0.01	0.076
BMI (kg/m^2)				
<18.5 (underweight)	0.05	−0.12	0.22	0.557
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	0.005	−0.06	0.07	0.880
>=30 (obese)	0.003	−0.08	0.08	0.948
Smoking status				
Non-smoker	[REF]			
Smoker	−0.06	−0.17	0.04	0.205
Ex-smoker	0.04	−0.02	0.10	0.230
Previous transplant				
No	[REF]			
Yes	0.04	−0.04	0.12	0.320
Pre-emptive transplantation				
No	[REF]			
Yes	0.03	−0.04	0.10	0.420

Table 6.7 shows the multivariable model for EQ-5D VAS scores. With all other variables held constant, EQ-5D VAS scores were predicted to be 6.75 units higher for LDKT recipients than DDKT recipients on a scale of 0-100 (95% CI 1.21, 12.30, p=0.017). The R^2 value for the model was 0.375, meaning the model explained 37.5% of variance in scores. Older patients (compared with younger patients), single patients (compared with married patients), patients with polycystic kidney disease (compared with diabetic nephropathy patients) and patients with a modified CCI score of 1 (compared to 0) reported significantly better EQ-5D VAS scores. Patients on long term sick leave and smokers reported significantly lower EQ-5D VAS scores.

Table 6.7. Multivariable analysis of factors associated with EQ-5D VAS				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	6.75	1.21	12.30	0.017
Age group				
18 – 34	[REF]			
35 – 49	8.64	0.16	17.12	0.046
50 – 64	10.60	1.15	20.06	0.028
65 – 75	10.76	-1.66	23.19	0.089
Gender				
Male	[REF]			
Female	-3.13	-8.49	2.22	0.249
Ethnicity				
White	[REF]			
Asian	-8.15	-17.89	1.59	0.100
Black	3.54	-9.51	16.60	0.592
Other	-1.40	-23.42	20.62	0.900
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	2.56	-4.44	9.56	0.471
Single	9.06	0.81	17.31	0.032
Qualifications				
Higher education level	[REF]			
Secondary education level	-0.86	-6.54	4.83	0.766
No qualifications	-2.16	-11.97	7.65	0.664
Employment status				
Employed	[REF]			
Unemployed	-7.72	-22.32	6.87	0.297
Long term sick / disability	-9.31	-16.39	-2.23	0.010
Retired	-2.77	-11.17	5.62	0.515
Other	4.25	-5.68	14.18	0.398
Car ownership				
Yes	[REF]			
No	-1.55	-11.23	8.12	0.751
Home ownership				
Yes	[REF]			
No	6.27	-0.86	13.40	0.084
Health literacy				
Normal	[REF]			
Limited	-2.47	-13.75	8.80	0.665
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	8.99	-3.84	21.81	0.168
Polycystic kidney disease	14.86	2.04	27.68	0.023
Pyelonephritis	13.67	-0.17	27.52	0.053

Hypertensive nephropathy	14.42	-1.83	30.68	0.082
Renal vascular disease	-17.57	-42.71	7.58	0.169
Other	12.55	-0.20	25.29	0.054
Uncertain	3.19	-11.37	17.75	0.665
Modified CCI				
0	[REF]			
1	11.17	1.25	21.09	0.028
2	1.30	-7.77	10.37	0.777
≥3	-4.96	-18.77	8.85	0.479
Mental illness				
No	[REF]			
Yes	-8.48	-19.24	2.28	0.122
BMI (kg/m^2)				
<18.5 (underweight)	-3.65	-19.42	12.12	0.648
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	0.55	-5.14	6.25	0.848
>=30 (obese)	-1.86	-9.28	5.57	0.622
Smoking status				
Non-smoker	[REF]			
Smoker	-9.58	-18.72	-0.45	0.040
Ex-smoker	-3.86	-9.72	2.00	0.195
Previous transplant				
No	[REF]			
Yes	-0.07	-7.77	7.63	0.986
Pre-emptive transplantation				
No	[REF]			
Yes	-3.74	-10.09	2.61	0.246

The multivariable model for WBQ12 scores is shown in Table 6.8. WBQ12 scores were 2.58 units higher for LDKT recipients than DDKT recipients on a scale of 0 to 36 (95% CI 0.22, 4.95, p=0.033) with adjustment for all other factors in the model. The R^2 value for the model was 0.424. The model also showed that wellbeing scores were significantly worse for females, Asian patients and patients with mental illness. Patients with glomerulonephritis, polycystic kidney disease, pyelonephritis and hypertensive nephropathy reported significantly better wellbeing than patients with diabetic nephropathy as the primary renal disease.

Table 6.8. Multivariable analysis of factors associated with WBQ12				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	2.58	0.22	4.95	0.033
Age group				
18 – 34	[REF]			
35 – 49	-0.12	-3.74	3.50	0.946
50 – 64	-0.03	-4.07	4.01	0.988
65 – 75	1.45	-3.86	6.76	0.590
Gender				
Male	[REF]			
Female	-2.70	-4.99	-0.42	0.021
Ethnicity				
White	[REF]			
Asian	-4.20	-8.36	-0.04	0.048
Black	3.93	-1.65	9.50	0.166
Other	2.08	-7.32	11.49	0.662
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	0.75	-2.24	3.74	0.622
Single	2.78	-0.74	6.30	0.121
Qualifications				
Higher education level	[REF]			
Secondary education level	0.73	-1.70	3.15	0.553
No qualifications	1.25	-2.94	5.44	0.555
Employment status				
Employed	[REF]			
Unemployed	-3.85	-10.08	2.39	0.225
Long term sick / disability	-0.81	-3.83	2.21	0.596
Retired	1.84	-1.74	5.43	0.311
Other	0.73	-3.51	4.97	0.733
Car ownership				
Yes	[REF]			
No	3.69	-0.44	7.83	0.079
Home ownership				
Yes	[REF]			
No	-1.66	-4.70	1.39	0.284
Health literacy				
Normal	[REF]			
Limited	-0.90	-5.72	3.91	0.712
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	7.89	2.41	13.37	0.005
Polycystic kidney disease	8.07	2.60	13.55	0.004
Pyelonephritis	8.90	2.99	14.82	0.004

Hypertensive nephropathy	8.08	1.14	15.02	0.023
Renal vascular disease	2.20	−8.54	12.94	0.686
Other	9.11	3.66	14.55	0.001
Uncertain	2.65	−3.57	8.86	0.401
Modified CCI				
0	[REF]			
1	4.02	−0.22	8.25	0.063
2	1.13	−2.75	5.00	0.565
≥3	−0.89	−6.79	5.00	0.765
Mental illness				
No	[REF]			
Yes	−9.32	−13.91	−4.72	0.0001
BMI (kg/m^2)				
<18.5 (underweight)	3.13	−3.61	9.86	0.360
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	1.60	−0.84	4.03	0.196
>=30 (obese)	0.20	−2.97	3.37	0.900
Smoking status				
Non-smoker	[REF]			
Smoker	−1.98	−5.89	1.92	0.316
Ex-smoker	−0.51	−3.02	1.99	0.685
Previous transplant				
No	[REF]			
Yes	2.71	−0.57	6.00	0.105
Pre-emptive transplantation				
No	[REF]			
Yes	−0.27	−2.98	2.44	0.844

Table 6.9 shows the multivariable analysis of factors associated with general QoL. With all other variables held constant, general QoL scores were 0.41 units higher for LDKT recipients than DDKT recipients on a scale of -3 to +3 (95% CI 0.06, 0.75, p=0.022). The R^2 value for the model was 0.415. General QoL was significantly worse for unemployed patients, patients on long term sick leave or not working due to disability, those with a higher CCI score and patients with mental illness. Single patients reported significantly better general QoL than married or cohabiting patients.

Table 6.9. Multivariable analysis of factors associated with general QoL				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	0.41	0.06	0.75	0.022
Age group				
18 – 34	[REF]			
35 – 49	-0.08	-0.60	0.44	0.764
50 – 64	-0.39	-0.96	0.19	0.187
65 – 75	-0.17	-0.94	0.60	0.660
Gender				
Male	[REF]			
Female	-0.21	-0.55	0.12	0.204
Ethnicity				
White	[REF]			
Asian	-0.38	-0.99	0.23	0.218
Black	0.48	-0.34	1.29	0.247
Other	-0.06	-1.44	1.31	0.931
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	0.32	-0.12	0.76	0.149
Single	0.52	0.01	1.03	0.045
Qualifications				
Higher education level	[REF]			
Secondary education level	-0.05	-0.40	0.31	0.794
No qualifications	0.46	-0.15	1.07	0.137
Employment status				
Employed	[REF]			
Unemployed	-1.08	-1.99	-0.16	0.021
Long term sick / disability	-0.50	-0.94	-0.06	0.027
Retired	0.35	-0.18	0.87	0.194
Other	0.43	-0.18	1.03	0.164
Car ownership				
Yes	[REF]			
No	-0.21	-0.81	0.40	0.501
Home ownership				
Yes	[REF]			
No	-0.24	-0.68	0.21	0.291
Health literacy				
Normal	[REF]			
Limited	0.14	-0.57	0.84	0.703
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	0.44	-0.37	1.24	0.284
Polycystic kidney disease	0.47	-0.33	1.27	0.245
Pyelonephritis	0.005	-0.86	0.87	0.991

Hypertensive nephropathy	0.80	−0.22	1.81	0.123
Renal vascular disease	−1.07	−2.64	0.50	0.180
Other	0.48	−0.31	1.28	0.234
Uncertain	−0.04	−0.95	0.87	0.929
Modified CCI				
0	[REF]			
1	0.33	−0.29	0.95	0.295
2	−0.62	−1.18	−0.05	0.033
≥3	−0.44	−1.31	0.42	0.310
Mental illness				
No	[REF]			
Yes	−0.86	−1.53	−0.19	0.013
BMI (kg/m^2)				
<18.5 (underweight)	0.25	−0.73	1.24	0.615
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	0.08	−0.27	0.44	0.654
>=30 (obese)	−0.12	−0.58	0.35	0.613
Smoking status				
Non-smoker	[REF]			
Smoker	−0.25	−0.82	0.32	0.383
Ex-smoker	0.01	−0.36	0.37	0.964
Previous transplant				
No	[REF]			
Yes	0.31	−0.18	0.79	0.211
Pre-emptive transplantation				
No	[REF]			
Yes	0.33	−0.06	0.72	0.101

Table 6.10 shows the multivariable model for RDQoL. With adjustment for all other variables, RDQoL scores were predicted to be 0.95 units higher for LDKT recipients than DDKT recipients on a scale of -9 to +3 (95% CI 0.29, 1.61, p=0.005). The R^2 value for the model was 0.444. Asian patients and patients with mental illness reported significantly worse renal dependent QoL, while overweight and obese patients reported significantly better RDQoL scores.

Table 6.10. Multivariable analysis of factors associated with RDQoL				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	0.95	0.29	1.61	0.005
Age group				
18 – 34	[REF]			
35 – 49	−0.30	−1.29	0.69	0.552
50 – 64	−0.14	−1.25	0.96	0.795
65 – 75	0.08	−1.39	1.55	0.916
Gender				
Male	[REF]			
Female	−0.14	−0.78	0.49	0.654
Ethnicity				
White	[REF]			
Asian	−3.06	−4.22	−1.90	<0.0001
Black	−1.04	−2.59	0.51	0.188
Other	−0.13	−2.75	2.49	0.922
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	−0.03	−0.86	0.80	0.944
Single	0.94	−0.04	1.91	0.059
Qualifications				
Higher education level	[REF]			
Secondary education level	−0.48	−1.15	0.19	0.162
No qualifications	0.25	−0.92	1.41	0.677
Employment status				
Employed	[REF]			
Unemployed	0.18	−1.56	1.91	0.842
Long term sick / disability	0.19	−0.65	1.04	0.650
Retired	0.79	−0.21	1.79	0.118
Other	1.14	−0.01	2.30	0.052
Car ownership				
Yes	[REF]			
No	1.15	0.003	2.30	0.051
Home ownership				
Yes	[REF]			
No	−0.15	−1.00	0.70	0.723
Health literacy				
Normal	[REF]			
Limited	−0.33	−1.68	1.01	0.624
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	0.16	−1.37	1.69	0.837
Polycystic kidney disease	0.32	−1.20	1.85	0.675
Pyelonephritis	0.72	−0.93	2.37	0.387

Hypertensive nephropathy	−0.24	−2.18	1.69	0.803
Renal vascular disease	0.11	−2.89	3.10	0.945
Other	1.01	−0.51	2.52	0.192
Uncertain	0.02	−1.71	1.76	0.977
Modified CCI				
0	[REF]			
1	0.26	−0.92	1.44	0.666
2	0.50	−0.58	1.58	0.365
≥3	0.68	−0.97	2.32	0.417
Mental illness				
No	[REF]			
Yes	−2.47	−3.75	−1.19	0.0002
BMI (kg/m^2)				
<18.5 (underweight)	0.51	−1.37	2.39	0.593
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	0.84	0.16	1.52	0.016
>=30 (obese)	1.05	0.16	1.93	0.021
Smoking status				
Non-smoker	[REF]			
Smoker	−0.41	−1.50	0.67	0.453
Ex-smoker	−0.26	−0.96	0.44	0.468
Previous transplant				
No	[REF]			
Yes	−0.36	−1.28	0.55	0.436
Pre-emptive transplantation				
No	[REF]			
Yes	0.04	−0.71	0.79	0.909

The multivariable model for RTSQs is shown in Table 6.11. RTSQs scores were 7.06 units higher for LDKT recipients than DDKT recipients on a scale of 0 to 78 (95% CI 3.96, 10.16, p<0.0001), after adjustment for all other variables. The R^2 value for the model was 0.429. Patients with no qualifications and limited health literacy reported significantly better RTSQs scores. Patients with a modified CCI score of 2, patients with mental illness and those who received a pre-emptive transplant (borderline significance p=0.051) reported worse satisfaction with their transplant.

Table 6.11. Multivariable analysis of factors associated with RTSQs				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	7.06	3.96	10.16	<0.0001
Age group				
18 – 34	[REF]			
35 – 49	0.80	-3.95	5.54	0.740
50 – 64	2.98	-2.30	8.27	0.266
65 – 75	5.78	-1.17	12.74	0.102
Gender				
Male	[REF]			
Female	-0.15	-3.14	2.85	0.922
Ethnicity				
White	[REF]			
Asian	-5.27	-10.72	0.17	0.058
Black	3.86	-3.45	11.16	0.298
Other	-1.94	-14.25	10.38	0.756
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	2.88	-1.04	6.79	0.149
Single	2.15	-2.47	6.76	0.359
Qualifications				
Higher education level	[REF]			
Secondary education level	0.77	-2.41	3.95	0.633
No qualifications	8.44	2.95	13.93	0.003
Employment status				
Employed	[REF]			
Unemployed	-7.80	-15.97	0.36	0.061
Long term sick / disability	-3.18	-7.14	0.78	0.115
Retired	-2.42	-7.12	2.28	0.310
Other	2.70	-2.85	8.26	0.338
Car ownership				
Yes	[REF]			
No	-1.71	-7.12	3.71	0.534
Home ownership				
Yes	[REF]			
No	0.50	-3.49	4.49	0.805
Health literacy				
Normal	[REF]			
Limited	7.18	0.87	13.48	0.026
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	2.94	-4.23	10.12	0.418
Polycystic kidney disease	1.20	-5.97	8.37	0.742
Pyelonephritis	1.87	-5.88	9.62	0.634

Hypertensive nephropathy	4.74	-4.36	13.83	0.305
Renal vascular disease	-1.77	-15.83	12.30	0.804
Other	5.98	-1.15	13.11	0.100
Uncertain	-1.14	-9.29	7.00	0.782
Modified CCI				
0	[REF]			
1	5.10	-0.45	10.65	0.071
2	-6.56	-11.64	-1.49	0.012
≥3	4.03	-3.69	11.75	0.304
Mental illness				
No	[REF]			
Yes	-8.02	-14.04	-2.00	0.009
BMI (kg/m^2)				
<18.5 (underweight)	-8.72	-17.54	0.10	0.053
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	2.19	-0.99	5.38	0.176
>=30 (obese)	1.17	-2.98	5.32	0.578
Smoking status				
Non-smoker	[REF]			
Smoker	-4.92	-10.03	0.19	0.059
Ex-smoker	-1.90	-5.18	1.37	0.253
Previous transplant				
No	[REF]			
Yes	-0.16	-4.47	4.15	0.942
Pre-emptive transplantation				
No	[REF]			
Yes	-3.54	-7.10	0.01	0.051

Table 6.12 shows the results of the multivariable model for RTSQc. With all other variables held constant, RTSQc scores were 6.40 units higher for LDKT recipients than DDKT recipients on a scale of -39 to +39 (95% CI 2.44, 10.36, p=0.0002). The R^2 value for the model was 0.430. Unemployed patients, those with a modified CCI score of 2, underweight patients and patients who underwent pre-emptive transplantation reported significantly worse RTSQc scores, while patients with limited health literacy and hypertensive nephropathy reported significantly better scores.

Table 6.12. Multivariable analysis of factors associated with RTSQc				
Variable	**Parameter estimate**	**95% CI**		**p-value**
Transplant type				
DDKT	[REF]			
LDKT	6.40	2.44	10.36	0.002
Age group				
18 – 34	[REF]			
35 – 49	1.97	-4.04	7.97	0.518
50 – 64	5.26	-1.37	11.88	0.119
65 – 75	3.97	-4.78	12.73	0.371
Gender				
Male	[REF]			
Female	0.47	-3.39	4.33	0.810
Ethnicity				
White	[REF]			
Asian	-0.86	-7.66	5.95	0.804
Black	3.19	-5.93	12.31	0.490
Other	-2.35	-17.77	13.07	0.764
Civil status				
Married / Living with partner	[REF]			
Divorced / Separated / Widowed	5.00	-0.13	10.12	0.056
Single	4.50	-1.34	10.34	0.130
Qualifications				
Higher education level	[REF]			
Secondary education level	-0.02	-4.09	4.05	0.991
No qualifications	3.90	-3.11	10.90	0.273
Employment status				
Employed	[REF]			
Unemployed	-13.49	-24.70	-2.28	0.019
Long term sick / disability	-4.71	-9.76	0.34	0.068
Retired	-2.94	-8.86	2.98	0.328
Other	2.90	-4.02	9.82	0.408
Car ownership				
Yes	[REF]			
No	-5.04	-12.17	2.10	0.165
Home ownership				
Yes	[REF]			
No	-0.32	-5.34	4.71	0.901
Health literacy				
Normal	[REF]			
Limited	10.20	1.81	18.59	0.018
Primary renal disease				
Diabetic nephropathy	[REF]			
Glomerulonephritis	4.21	-4.82	13.24	0.358
Polycystic kidney disease	0.43	-8.65	9.50	0.926
Pyelonephritis	0.20	-9.58	9.98	0.968

Hypertensive nephropathy	11.94	0.54	23.35	0.040
Renal vascular disease	1.78	−16.00	19.55	0.844
Other	7.76	−1.14	16.66	0.087
Uncertain	2.39	−7.94	12.72	0.648
Modified CCI				
0	[REF]			
1	4.58	−2.37	11.53	0.195
2	−10.59	−16.93	−4.25	0.001
≥3	4.95	−4.77	14.67	0.315
Mental illness				
No	[REF]			
Yes	−6.45	−13.97	1.07	0.092
BMI (kg/m²)				
<18.5 (underweight)	−12.79	−23.79	−1.80	0.023
18.5 – 24.9 (normal)	[REF]			
25.0 – 29.9 (overweight)	1.95	−2.16	6.06	0.349
>=30 (obese)	3.41	−1.86	8.68	0.203
Smoking status				
Non-smoker	[REF]			
Smoker	1.11	−5.32	7.55	0.733
Ex-smoker	−3.90	−8.07	0.28	0.067
Previous transplant				
No	[REF]			
Yes	0.43	−5.01	5.87	0.876
Pre-emptive transplantation				
No	[REF]			
Yes	−10.43	−15.02	−5.84	<0.0001

A summary of PROMS outcomes for LDKT vs DDKT recipients from the multivariable models is shown in Table 6.13. Except for the EQ-5D utility questionnaire, all other PROMS questionnaires demonstrated better outcomes for LDKT compared with DDKT recipients in adjusted multivariable models.

Table 6.13. PROMS for LDKT vs DDKT recipients from adjusted multivariable models

PROMS	Parameter estimates LDKT vs DDKT (ref)	95% CI	p-value
EQ-5D Utility	0.04	[-0.02, 0.10]	0.231
EQ-5D VAS	6.75	[1.21, 12.30]	0.017
WBQ12	2.58	[0.22, 4.95]	0.033
General QoL	0.41	[0.06, 0.75]	0.022
RDQoL	0.95	[0.29, 1.61]	0.005
RTSQs	7.06	[3.96, 10.16]	<0.0001
RTSQc	6.40	[2.44, 10.36]	0.002

6.4. Discussion

In this study, a wide range of general and condition-specific PROMS were assessed in a cohort of kidney transplant recipients. At 1 year post-transplantation, LDKT recipients reported significantly better health status, wellbeing, general quality of life, renal-dependent quality of life and renal treatment satisfaction compared with DDKT recipients, after adjustment for demographic, socioeconomic and clinical variables.

Previous research on PROMS in patients with ESRD has focussed heavily patient health status, otherwise known as health-related quality of life or health utilities. Health status measures the patient's perceived impact of their health on a number of domains including physical, social and emotional functions. Health status is often the measure of choice as it enables the calculation of quality-adjusted life years for cost-effectiveness analyses, which in turn leads to the potential to influence resource allocation.[284] The most widely used health status questionnaires include the EQ-5D and the 36-Item Short Form Health Survey (SF-36). In this study we chose to use the EQ-5D as it is recommended as the preferred instrument for measuring health status by the National Institute for Health and Care Excellence (NICE)[285] and has been validated in renal transplant recipients.[286] The benefits of transplantation over dialysis on patient reported health status are widely acknowledged.[63, 103, 276] While dialysis patients demonstrate substantially worse health status compared with the general population, transplantation seems to restore health status to a level comparable to the general population.[287] However, only few studies have compared the health status of patients

receiving kidney transplants from different donor types. De Groot et al. examined health status among LDKT and DDKT recipients in Leiden using the SF-36 and found that LDKT recipients had better health status than DDKT recipients, but only for the physical component score (not the mental component score).[288] Griva et al. also used the SF-36 to compare health status between LDKT and DDKT recipients in London, but found no differences between the two groups.[104] In the present study, there were no significant differences in health status between LDKT and DDKT recipients when measured by the EQ-5D questionnaire, however LDKT recipients did report higher EQ-5D VAS scores. The finding that EQ-5D VAS scores were better for LDKT than DDKT recipients cannot be explained by a higher rate of graft failure within the DDKT group as no patients within the entire subset experienced graft failure within the first year. Furthermore, the multivariable analyses were corrected for sociodemographic and comorbidity differences between the two groups to minimise the risk of confounding. Patient reported health status has been shown to be an independent predictor of mortality in kidney transplant recipients, even after adjustment for clinical variables.[289, 290] It has been suggested that a patient's own subjective assessment of their health status may reflect their real health situation better than objective parameters, and as such should be considered as an important factor when assessing patient prognosis.[289]

Health status questionnaires in isolation may not be a reliable indicator of a patient's overall quality of life as they do not capture many other non-health related aspects of life which may be important to patients. Therefore, in this

study we also considered other PROMS to ensure a multi-dimensional approach.

Poor psychological well-being has been reported to be an important predictor of compliance to post-transplantation immunosuppressive therapy, renal function and graft rejection.[96, 291] We used the WBQ-12 questionnaire to assess well-being as it has previously been shown to be a reliable and valid measure of psychological well-being in various popultions[280, 281, 292, 293] including patients with ESRD.[294] Well-being scores were significantly higher at 1 year post-transplantation for LDKT versus DDKT recipients. This is consistent with a previous study by Gozdowska et al. which showed that LDKT recipients reported a better sense of happiness, better social life involvement and were more satisfied with their interpersonal relationships compared with DDKT recipients.[295] The authors surmised that a greater level of social support improved recipients ability to adapt to post-transplantation life and increased the recipients' level of happiness.[295] Other research has also linked having better social support with an enhanced ability to recover and adapt after transplantation.[96, 296, 297] One study described higher levels of guilt towards the donor among LDKT compared with DDKT recipients, when measured with the Transplant Effects Questionnaire.[104] However the study did not assess whether this translated into a detrimental effect on overall well-being. Lumsdaine et al. analysed levels of anxiety towards the donor among LDKT recipients at different time points.[105] Pre-operatively LDKT recipients did express a high level of concern about their donor, but this significantly decreased at 6 weeks and 1 year post-transplantation. Furthermore, despite their anxiety about the donor, LDKT recipients had excellent overall

psychological well-being at 6 weeks and 1 year post-transplantation, with scores that were significantly higher than the UK normative value. The same study also reported that both donors and recipients experienced significant improvements in their mutual relationship after LDKT.[105] It is important not to forget about the potential psychological effects of LDKT on the donor. A systematic review of over 5000 living kidney donors found that the large majority of donors derived positive psychological benefits, felt happier after donation and would choose to donate again.[298] Our study supports the theory that LDKT recipients may gain greater psychosocial benefits from transplantation than DDKT recipients, due to the process of receiving an organ from a person within their social support network, strengthening their interpersonal relationships, coping strategies and psychological well-being.

Both general QoL and renal-dependent QoL were found to be significantly higher for LDKT versus DDKT recipients after adjustment for confounding variables. As previously mentioned, most publications that state they have measured QOL have actually used tools that measure health status. There is a lack of evidence in the transplant literature for true QoL outcomes that encompass the multi-dimensional aspects of QoL. One study investigated QoL among transplant recipients using the World Health Organisation Quality of Life abbreviated version (WHOQOL-BREF), which assesses generic QoL in the four domains of physical health, psychological health, social relationships and environment. LDKT recipients reported significantly higher scores in the psychological and environmental domains compared with DDKT recipients.[295] Disease specific PROMS can provide more detailed and relevant outcomes for the intended study population. In this study we utilised the RDQoL which

assesses the impact of renal disease on various aspects of a patient's life relevant to their disease such as dietary and fluid restrictions, physical appearance, work, future, family life, physical capability, travel, holidays, sex life, confidence, social life, dependence etc.[282] We did not find any other published studies that have compared disease-specific QoL outcomes between LDKT and DDKT recipients and were therefore unable to compare our results with other research. This highlights the great need for more research in this area.

Another important aim in the care of patients with ESRD is treatment satisfaction. This gives an idea of the patient's overall experience of their treatment and thus is an important tool for identifying ways in which to improve patient care. The RTSQs and RTSQc assess ESRD patients' satisfaction with various aspects of their treatment including convenience, flexibility, freedom and satisfaction to continue with the treatment.[283] Treatment satisfaction has previously been shown to be significantly better for transplant recipients compared with patients on dialysis.[101, 283] However, to our knowledge this is the first study to show that LDKT recipients express significantly greater satisfaction with their treatment compared with DDKT recipients. Patient satisfaction with their treatment is vital to ensure optimal adherence to the treatment regimen including immunosuppressive medications and has been shown to have a direct association with the success of the graft.[97, 299] Investigating the reasons why LDKT recipients report better treatment satisfaction then DDKT recipients was beyond the scope of this study. However, the more timely access to transplantation, avoidance or minimisation of dialysis, the planned elective operation, higher quality graft,

reduced cold ischaemic time and superior graft and patient survival outcomes would all be plausible reasons for a better patient treatment experience in LDKT. The analysis also demonstrated that patients who underwent pre-emptive transplantation reported worse treatment satisfaction compared with patients who underwent transplantation after a period of dialysis, particularly for the RTSQc questionnaire (satisfaction with current versus previous treatment). This finding is unsurprising, given the fact that pre-emptive recipients have proceeded from having no treatment to undergoing a major operation, immunosuppression and experiencing the associated potential complications. Studies have consistently shown that transplantation results in better PROMS than dialysis, due to lower levels of physical and psychological morbidity and improved lifestyle.[9, 10, 63] However, pre-emptive transplant recipients have not experienced the burdens of dialysis and thus cannot appreciate the benefits of transplantation over dialysis. This is concerning because in most countries including the UK, pre-emptive transplantation is accepted as the preferred treatment option due to its superior graft and patient survival rates.[21, 300-302] These findings highlight the need for improved efforts to educate patients about the benefits of pre-emptive transplantation, to manage patient expectations and to provide psychological support throughout the whole treatment journey. It is encouraging however, that pre-emptive transplantation did not appear to be detrimental to patients' health status, psychological well-being and quality of life, compared with other transplant recipients.

The results of this study should be interpreted within the context of some limitations. First, the PROMS data were from a fixed time point of 1 year post-

transplantation, and we were unable to consider changes in PROMS over time. Thus, the results must be verified in a longitudinal study. Second, all of the patients who returned the questionnaires had a functioning graft, and as such the results of the study may not be representative for patients who experienced graft failure. Response bias is a recognised limitation of PROMS, because patients with poorer outcomes are less likely to engage and respond.[303] This must be taken into account when interpreting the results, as outcomes may have been overestimated in both groups. Third, we were unable to explore the reasons for differences in PROMS between the two recipient groups within the limits of this study. One of the potential reasons for better PROMS in LDKT could be superior graft function. Unfortunately, we were not able to correct the analyses for graft function as we did not have access to graft function data. If correcting for graft function eliminates the differences in PROMS between LDKT and DDKT, this implies that the better outcomes are due to better graft function. If differences were to remain despite adjusting for graft function, then other parts of the transplantation pathway may be implicated in determining PROMS. This should be addressed in future work. The strengths of this study are that we included patients from all transplant units in the UK, there was a high questionnaire response rate (81.7%) and all analyses were adjusted for an extensive set of variables.

The results of this study support the promotion of LDKT as an excellent treatment option for patients with ESRD. LDKT is associated with superior PROMS compared with DDKT recipients at 1 year post transplantation. Further work is needed to determine the reasons for these differences, and

whether targeted interventions can improve outcomes for disadvantaged patient groups.

CHAPTER 7

Prediction of Survival on Dialysis

7.1. Introduction

Patients on long-term dialysis for the treatment of end-stage renal disease (ESRD) experience drastically reduced life expectancy, but there is wide variation in the prognosis of individual patients. In the UK, the median life expectancy for incident dialysis patients aged 25-29 years is approximately 18.5 years, while for patients over 75 years it is just 2.4. years.[304] The presence of comorbidity, and in particular complex and multimorbidity is an increasingly common problem in the dialysis population.[305] Previous studies have shown that comorbidity is major risk factor for mortality on dialysis and significantly contributes to the variability in patient survival.[90, 109, 306]

Risk stratification of patients on dialysis using predictive models can offer patients valuable prognostic information, as well as allowing clinicians to tailor clinical care and therapeutic decisions to individual patients. Risk scores can also guide research on targeted interventions for high risk patients and provide a useful method of adjusting for case-mix in research studies.

Various models aimed at predicting survival on dialysis have been developed, but few are utilised in clinical practice. Many studies have developed models using variables that are not readily available to clinicians e.g. peritoneal equilibration test and specific biomarkers such as plasma S100A12, or are restricted to patients on one type of dialysis therapy e.g. haemodialysis (HD) or peritoneal dialysis (PD) only and therefore unable to be applied to the entire incident dialysis population.[307-311] It is well recognised that dialysis outcomes vary significantly between different countries, and so models

developed in one dialysis population may not be applicable to other dialysis populations.[114] Furthermore, although comorbidity is included in most predictive models due to its strong effect on dialysis survival, collecting accurate comorbidity data at a population level is challenging and as such the majority of studies have used retrospective data, data obtained from administrative datasets or single centre data, resulting in loss of reliability.[92, 312-314]

Currently the average waiting time from activation on the transplant waiting list to transplantation is 2 years.[13] However, many patients will suffer clinical deterioration or death during the wait. A risk index that predicts which patients are likely to survive the first 2 years on dialysis would not only provide important prognostic information, but could also be used as a useful tool to inform decisions regarding access to the waiting list. If adopted nationally, this would essentially standardise the referral process for transplantation, thereby reducing well documented disparities in access to transplantation in the UK.[3-5, 315] The aim of this analysis was to develop and validate a risk index to predict 2 year survival for incident dialysis patients in the UK, using prospective national data collected as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme.

7.2. Methods

7.2.1. Study population

The ATTOM incident dialysis cohort formed the study population for this analysis. This comprised of 2623 patients recruited within 90 days of starting dialysis, from all 72 renal units in the UK. Patients aged between 18 - 75 years were eligible for recruitment. Full recruitment methods are detailed in Chapter 2. The total recruitment period lasted from 1st November 2011 to 31st March 2013. However, in each centre, recruitment took place over a 12-month period at any point during the total recruitment period. Because of this, the true proportion of patients recruited to the study is difficult to quantify due to differing start and end recruitment dates in each centre. To provide an approximation, we have calculated the study population as a proportion of the number of patients aged 18-75 years starting dialysis in the UK during the total recruitment period (48.6%), with the acknowledgement that this is an underestimation of the true figure (Figure 7.1). For the purposes of this analysis, patients whose renal function recovered so that they no longer required dialysis (n=63) or who died or were transplanted within the first 90 days (n=51) were excluded, leaving 2509 patients included in the final analysis.

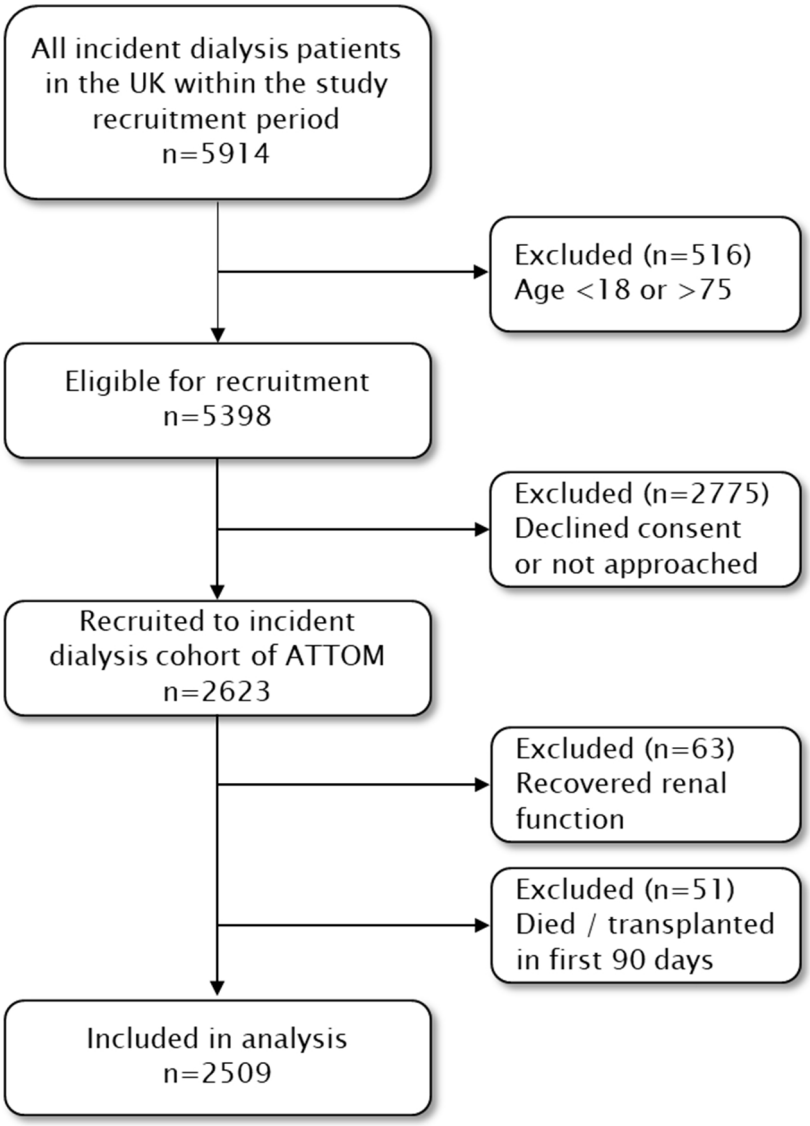

Figure 7.1. Study population

7.2.2. Study design and data variables

This was a prospective cohort study investigating the factors associated with survival on dialysis. Baseline demographic, clinical and comorbidity data were collected at the time of recruitment to the study (Appendix A.2.). Patients were followed up for 2 years from the start of dialysis.

The exposure variables of interest in this study were comorbidities present at the time of starting dialysis including diabetes, ischaemic heart disease, heart failure, atrial fibrillation, cardiac valve replacement, pacemaker, cerebrovascular disease, peripheral vascular disease, abdominal aortic aneurysm, chronic respiratory disease, chronic liver disease, blood borne viruses, malignancy, mental illness, dementia and body mass index (BMI) (definitions given in Appendix A.3.). BMI (kg/m^2) was grouped in accordance with the World Health Organisation (WHO) BMI classifications.[126] Other patient variables of interest included age, gender, ethnicity, primary renal disease, smoking status, previous transplantation, type of dialysis and albumin (g/L) (definitions in Appendix A.3.). Type of dialysis was categorised as HD (including haemodialysis and haemodiafiltration) and PD (including continuous ambulatory peritoneal dialysis and automated peritoneal dialysis).

The primary outcome measure was patient survival which was defined as the time from 90 days after starting dialysis to death, with censoring at the time of transplantation if a patient received a transplant, or at 2 years. This method for calculating survival on dialysis is designed to minimise the risk of including patients with acute renal failure, and is the method used by renal registries in most countries.[316] A secondary outcome measure was activation on the transplant waiting list. Time to listing was defined from the start of dialysis to the date of activation on the waiting list. Patients who were listed prior to the start of dialysis were given a time to listing of 0 days.

7.2.3. Statistical methods

Baseline characteristics were presented as numbers with percentages (%) and medians with interquartile ranges (IQR). Categorical data were compared by chi-squared tests and non-parametric continuous data were compared by Wilcoxon tests. The dataset was split evenly into derivation and validation datasets using Bernoulli trials, with each patient having a probability of 0.5 of being assigned to either dataset. The derivation dataset was used to identify patient level risk factors for survival on dialysis using univariable and multivariable Cox proportional hazards regression. The multivariable model was built using a manual backward elimination method, with all variables considered for inclusion in the model. The importance of each variable in the model was tested using the likelihood ratio test and variables with p-values <0.1 were retained in the model. Interaction terms were also considered for selection. Continuous variables were explored as linear, logarithmic, fractional polynomials and categorical variables. The proportional hazards assumption was tested using log cumulative hazards plots and Schoenfeld residuals and found to be satisfied for all variables. The presence of a renal unit effect was investigated by considering renal unit as a frailty effect. The proportion of missing data varied between 0% - 16% for all variables (Table 7.1). Missing data were imputed using the fully conditional specification logistic regression multiple imputation method to produce ten imputed datasets. Each imputed dataset was modelled separately, and parameter estimates were combined to create the final risk index. Two sensitivity analyses were conducted. The first used the same modelling methods as above in a sub-cohort of patients with no previous transplants. The second used a Fine and Gray model[317] to incorporate transplantation as a competing

risk when modelling time to patient death. The validation dataset was subsequently used to test the predictive ability of the derived model. The discrimination of the model was summarised using Harrell's c-statistic as well as plotting Kaplan-Meier (KM) survival estimates stratified by risk index quartile. Calibration of the model was assessed using the calibration-in-the-large and the calibration slope.[318] KM analysis was used to analyse the cumulative incidence of listing for each risk index quartile and to analyse the survival of listed versus non-listed patients. All analyses were conducted using SAS (version 9.4).

Table 7.1. Missing data

Variable	n [%]
Age	0 [0]
Gender	0 [0]
Ethnicity	10 [0.4]
Primary renal disease	25 [1.0]
Smoking status	380 [15.1]
Previous transplant	5 [0.2]
Type of dialysis	6 [0.2]
Albumin	285 [11.4]
Diabetes	20 [0.8]
Ischaemic heart disease	25 [1.0]
Heart failure	27 [1.1]
Atrial fibrillation	28 [1.1]
Cardiac valve replacement	28 [1.1]
Pacemaker	27 [1.1]
Cerebrovascular disease	27 [1.1]
Peripheral vascular disease	28 [1.1]
Abdominal aortic aneurysm	29 [1.2]
Chronic respiratory disease	27 [1.1]
Chronic liver disease	26 [1.1]
Blood borne viruses	26 [1.1]
Malignancy	23 [0.9]
Mental illness	25 [1.0]
Dementia	27 [1.1]
BMI	395 [15.7]

7.3. Results

7.3.1. Study population characteristics

The demographics of the study population were compared to those of all patients aged 18-75 years starting dialysis in the UK during the entire recruitment period using the one sample chi-square goodness of fit test (Table 7.2). Compared to the national incident dialysis population, the study population were younger and comprised a higher proportion of males, patients of White ethnicity and HD patients.

Table 7.2. Demographics of incident dialysis recipients – national population versus study population

Variable	National incident dialysis population	ATTOM incident dialysis population	p-value
Age			0.006
18 – 34	8.2	9.3	
35 – 49	19.8	20.5	
50 – 60	22.6	24.3	
60 – 70	31.5	29.8	
70 – 75	17.9	16.2	
Gender			0.008
Male	62.4	64.9	
Female	37.6	35.1	
Ethnicity			<0.0001
White	76.9	80.3	
Asian	12.3	11.3	
Black	8.2	7.1	
Other	2.6	1.3	
Dialysis modality			<0.0001
HD	75.1	79.1	
PD	24.9	20.9	

The study population was split evenly into derivation (50%) and validation (50%) datasets. The baseline prevalence of comorbidity (Table 7.3) and

baseline patient characteristics (Table 7.4) were compared between the derivation and validation datasets. Comorbidity prevalence was similar between the two datasets, with the most prevalent comorbidity being diabetes, followed by obesity, ischaemic heart disease and malignancy. There was a higher proportion of patients with abdominal aortic aneurysms in the derivation dataset. In both datasets, the median age was 58-59 years, and the majority of patients were male, of White ethnicity, had diabetes as the primary renal disease, were non-smokers and received HD as the modality of dialysis.

Table 7.3. Baseline comorbidity of the derivation and validation datasets

Variable	Derivation dataset [n=1263]	Validation dataset [n=1246]	p-value
Diabetes	535 [42.7]	499 [40.3]	0.226
Ischaemic heart disease	258 [20.7]	256 [20.7]	0.965
Heart failure	85 [6.8]	97 [7.9]	0.316
Atrial fibrillation	53 [4.3]	55 [4.5]	0.794
Cardiac valve replacement	14 [1.1]	17 [1.4]	0.568
Pacemaker	22 [1.8]	17 [1.4]	0.440
Cerebrovascular disease	108 [8.7]	121 [9.8]	0.322
Peripheral vascular disease	122 [9.8]	101 [8.2]	0.164
Abdominal aortic aneurysm	30 [2.4]	12 [1.0]	0.006
Chronic respiratory disease	137 [11.0]	163 [13.2]	0.091
Chronic liver disease	23 [1.8]	36 [2.9]	0.080
Blood borne viruses	36 [2.9]	32 [2.6]	0.654
Malignancy	153 [12.3]	177 [14.3]	0.134
Mental illness	108 [8.7]	110 [8.9]	0.819
Dementia	6 [0.5]	2 [0.2]	0.162
BMI, kg/m^2			0.060
Underweight (<18.5)	30 [2.8]	41[3.9]	
Normal (18.5 – 24.9)	353 [33.2]	371 [35.3]	
Overweight (25.0 – 29.9)	340 [32.0]	284 [27.0]	
Obese (≥30.0)	340 [32.0]	355 [33.8]	

Data are number [%].

Data are missing for some participants and excluded from percentage calculations.

Number of missing data are shown in Table 7.1.

p-value is for chi-square test.

Table 7.4. Baseline patient characteristics of the derivation and validation datasets

Variable	Derivation dataset [n=1263]	Validation dataset [n=1246]	p-value
Age	58.2 [47.2 – 66.7]	58.7 [47.8 – 67.5]	0.418
Gender			0.195
Male	835 [66.1]	793 [63.6]	
Female	428 [33.9]	453 [36.4]	
Ethnicity			0.090
White	995 [79.0]	1007 [81.2]	
Asian	156 [12.4]	128 [10.3]	
Black	85 [6.8]	93 [7.5]	
Other	23 [1.8]	12 [1.0]	
Primary renal disease			0.241
Polycystic kidney disease	91 [7.3]	107 [8.7]	
Diabetic nephropathy	353 [28.3]	337 [27.2]	
Glomerulonephritis	213 [17.1]	201 [16.3]	
Pyelonephritis	84 [6.7]	97 [7.8]	
Hypertensive nephropathy	82 [6.6]	82 [6.6]	
Renal vascular disease	55 [4.4]	33 [2.7]	
Other	177 [14.2]	193 [15.6]	
Uncertain	192 [15.4]	187 [15.1]	
Smoking status			0.108
Non-smoker	538 [50.0]	497 [47.2]	
Smoker	205 [19.1]	185 [17.6]	
Ex-smoker	333 [31.0]	371 [35.2]	
Previous transplant	139 [11.0]	130 [10.4]	0.629
Type of dialysis			0.169
HD	995 [79.0]	973 [78.2]	
PD	264 [21.0]	271 [21.8]	
Albumin	34 [30 – 38]	34.5 [30-38]	0.739

Data are median [IQR] or number [%].
Data are missing for some participants and excluded from percentage calculations.
Number of missing data are shown in Table 7.1.
Wilcoxon test for age and albumin, all others chi-square test.

7.3.2. Derivation of the ATTOM risk index

Two year follow-up data were available for all patients. In the derivation dataset, 179 (14.2%) patients died, 203 (16.1%) were censored at the time of transplantation and 881 (69.8%) were still alive at 2 years. Overall 2 year

survival calculated with the Kaplan-Meier method was 84.4% (95% confidence interval [CI] 82.2, 86.4). The impact of comorbidity and patient factors on 2 year survival were investigated in the derivation dataset with univariable analysis (Table 7.5 and Table 7.6), multivariable Cox regression using complete case data and subsequently multivariable Cox regression using imputed data in order to account for missing data and derive the risk index (Table 7.7). Through building the models on the 10 imputed datasets, it was observed that the models overall reflected the model derived from complete case analysis and the same terms were included in the final model combining all imputed datasets (Table 7.7).

Table 7.5. Univariable Cox regression analysis of comorbidities affecting 2 year patient survival on dialysis

Variables	HR	[95% CI]	p-value
Diabetes	1.55	[1.16, 2.09]	0.003
Ischaemic heart disease	1.69	[1.23, 2.32]	0.001
Heart failure	2.06	[1.33, 3.20]	0.001
Atrial fibrillation	2.39	[1.43, 3.99]	0.0009
Cardiac valve replacement	2.02	[0.75, 5.45]	0.163
Pacemaker	2.32	[1.09, 4.93]	0.029
Cerebrovascular disease	1.60	[1.04, 2.46]	0.032
Peripheral vascular disease	1.68	[1.12, 2.52]	0.012
Abdominal aortic aneurysm	1.11	[0.46, 2.70]	0.818
Chronic respiratory disease	1.93	[1.33, 2.81]	0.0006
Chronic liver disease	3.49	[1.84, 6.60]	0.0001
Blood borne viruses	0.72	[0.27, 1.95]	0.520
Malignancy	2.18	[1.54, 3.09]	<0.0001
Mental illness	1.70	[1.11, 2.61]	0.016
Dementia	.	.	.
BMI, kg/m^2	1		
Underweight (<18.5)	2.30	[1.13, 4.67]	0.021
Normal (18.5 – 24.9)	1 [ref]		
Overweight (25.0 – 29.9)	0.53	[0.34, 0.84]	0.007
Obese (≥30.0)	1.02	[0.70, 1.49]	0.927

CI; confidence interval, HR; hazard ratio, ref; reference

(.) number is 0 or too small to calculate

Table 7.6. Univariable Cox regression analysis of patient factors affecting 2 year patient survival on dialysis			
Variables	**HR**	**[95% CI]**	**p-value**
Age (per 10 years)	1.34	[1.18, 1.52]	<0.0001
Gender			
Male	1 [ref]		
Female	1.37	[1.02, 1.85]	0.037
Ethnicity			
White	1 [ref]		
Asian	0.71	[0.43, 1.16]	0.166
Black	0.36	[0.15, 0.87]	0.024
Other	0.61	[0.15, 2.45]	0.483
Primary renal disease			
Polycystic kidney disease	1 [ref]		
Diabetic nephropathy	3.17	[1.28, 7.87]	0.013
Glomerulonephritis	1.49	[0.56, 3.99]	0.427
Pyelonephritis	2.21	[0.77, 6.35]	0.142
Hypertensive nephropathy	1.76	[0.59, 5.24]	0.313
Renal vascular disease	3.40	[1.18, 9.79]	0.023
Other	2.73	[1.06, 7.05]	0.038
Uncertain	2.17	[0.83, 5.65]	0.113
Smoking status			
Non-smoker	1 [ref]		
Smoker	1.46	[0.98, 2.18]	0.064
Ex-smoker	1.09	[0.75, 1.59]	0.640
Previous transplant	0.82	[0.50, 1.35]	0.438
Type of dialysis			
HD	1 [ref]		
PD	0.70	[0.47, 1.06]	0.090
Albumin, g/L (per unit increase)	0.92	[0.90, 0.94]	<0.0001

CI; confidence interval, HR; hazard ratio, ref; reference

During the multivariable modelling process (Table 7.7) the diabetes variable was explored in the following ways: any diagnosis of diabetes, diabetic nephropathy, diabetes as comorbidity only (excluding diabetic nephropathy), type 1 diabetes and type 2 diabetes. Diabetic nephropathy provided the best fit in the model after adjustment for all other factors. An interaction between age and diabetic nephropathy was also noted to be significant and was included in the model. This showed that the negative effect of increasing age

on survival was only significant for patients without diabetic nephropathy. For patients with diabetic nephropathy, there was little additional impact of age on survival, over and above the effect of diabetes. The albumin variable was found to fit best within the model using a natural logarithmic scale. The BMI variable was explored as a linear variable and as a categorical variable. Being underweight was noted to cause a negative effect on survival, whereas there was no difference in survival between normal, overweight and obese patients. Therefore, the best fit in the model was obtained using a binary variable for being underweight. Adding renal unit as a frailty effect in the model did not show any significant difference in patient survival between units (change in -2 log-likelihood p=0.987).

Table 7.7. Multivariable Cox regression analysis of factors affecting 2 year patient survival on dialysis			
Variables	**HR**	**[95% CI]**	**p-value**
Age (per 10 years)	.	.	<0.0001
Gender			
Male	1 [ref]		
Female	1.46	[1.07, 2.00]	0.017
Diabetic nephropathy			
No	.		
Yes	.	.	0.0002
Age*Diabetic nephropathy			0.013
Diabetic nephropathy Yes vs No at age=56	1.98	[1.39, 2.82]	
10 year increase in age when Diabetic nephropathy=No	1.46	[1.21, 1.75]	
10 year increase in age when Diabetic nephropathy=Yes	0.90	[0.73, 1.12]	
Log albumin, g/L (per unit)	0.20	[0.11, 0.36]	<0.0001
Heart failure			
No	1 [ref]		
Yes	1.72	[1.07, 2.77]	0.025
Atrial fibrillation			
No	1 [ref]		
Yes	1.65	[0.95, 2.87]	0.074
Chronic respiratory disease			
No	1 [ref]		
Yes	1.61	[1.09, 2.39]	0.017
Chronic liver disease			
No	1 [ref]		
Yes	2.57	[1.25, 5.27]	0.010
Malignancy			
No	1 [ref]		
Yes	2.01	[1.37, 2.93]	0.0003
Underweight (BMI<18.5kg/m²)			
No	1 [ref]		
Yes	2.13	[1.00, 4.53]	0.050

CI; confidence interval, HR; hazard ratio, ref; reference

Sensitivity analysis omitting patients with previous transplants had no effect on the terms included in the model. Similarly, using a competing risk model with transplantation as a competing risk had little effect on the resulting

parameter estimates. Therefore, the model developed in Table 7.7 was used to derive the equation for the ATTOM risk index (Table 7.8).

Table 7.8. ATTOM risk index for prediction of survival on dialysis

Risk index = Age/10 x 0.376
+Female x 0.381
+Diabetic nephropathy x 3.169
−Age/10 x Diabetic nephropathy x 0.452
−ln(albumin) x 1.597
+Heart failure x 0.543
+Atrial fibrillation x 0.503
+Chronic respiratory disease x 0.479
+Chronic liver disease x 0.943
+Malignancy x 0.696
+Underweight x 0.756

In order to use the risk index to predict 2 year survival on dialysis for a specific individual the following equation is used:

$$S_0(t)^{\exp(\Sigma\beta X - \Sigma\beta \bar{X})}$$

Where $S_0(t)$ is the baseline survival at t=2 years, $\Sigma\beta X$ is the risk index for the individual and $\Sigma\beta\bar{X}$ is the baseline risk index (calculated using mean values for continuous variables and 0 values for categorical variables). Using the derivation dataset, the baseline survival is calculated as 0.916 at 2 years and the baseline risk index is calculated as -3.487. A theoretical patient is provided as an example of calculating the predicted survival for a specific individual at the time of starting dialysis. The example patient is aged 63 years, male, with diabetic nephropathy, an albumin of 31g/L and heart failure,

but no other comorbidities and is overweight. The risk index for this patient is calculated using the equation in Table 7.8 as follows:

Risk index = (Age (63)/10 x 0.376) + (Female (0) x 0.381) + (Diabetic nephropathy (1) x 3.169) – (Age (63)/10 x Diabetic nephropathy (1) x 0.452) – (ln(albumin) (3.434) x 1.597) + (Heart failure (1) x 0.543) + (Atrial fibrillation (0) x 0.503) + (Chronic respiratory disease (0) x 0.479) + (Chronic liver disease (0) x 0.943) + (Malignancy x (0) 0.696) + (Underweight x (0) 0.756) = −2.251

Therefore the predicted survival is calculated as:

$0.916^{\exp(-2.251 - -3.487)} = 0.739$ (or 73.9%)

7.3.3. Validation of the ATTOM risk index

In the validation dataset, survival data were available for all patients. Over the 2 year follow up period, 188 (15.1%) patients died, 185 (14.8%) were censored at the time of transplantation and 873 (70.1%) were still alive at 2 years. Overall 2 year survival calculated with the KM estimator was 83.5% (95% CI 81.2, 85.5). The risk index (Table 7.8) was calculated for all patients in the validation dataset. Using the risk index to predict survival demonstrated a HR of 2.31 (95% 1.93, 2.77, p<0.0001) and c-statistic of 0.72, confirming reasonable discrimination of the model. The risk index values were then split into quartiles, with quartile 1 containing the lowest risk patients and quartile 4 containing the highest risk patients. KM survival estimates of survival stratified by risk index quartiles were compared (Figure 7.2). This confirmed good ability of the risk index to discriminate between patients with a low and high risk of mortality (p<0.0001). Calibration of the model was good with a

calibration-in-the-large of 18.2% vs 16.5% for predicted vs observed risk of death, and a calibration slope of 0.84 (standard error [SE] 0.09).

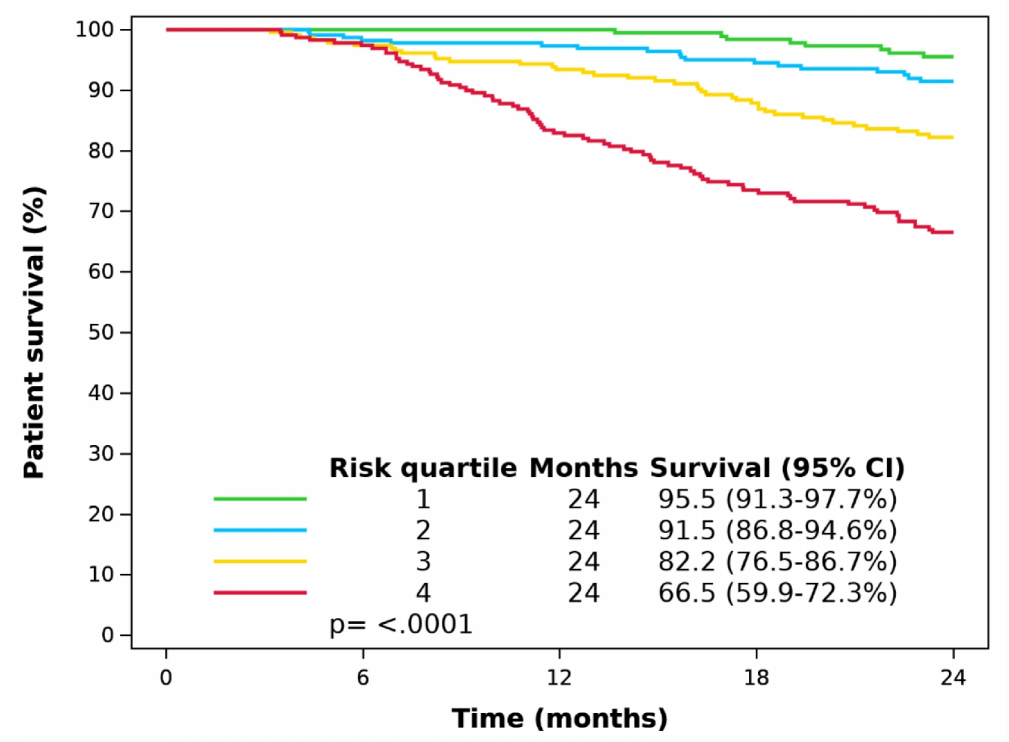

Figure 7.2. KM survival plot for effect of the risk index on 2 year patient survival on dialysis

7.3.4. Comparison of the risk index to the Charlson Comorbidity Index

In order to further assess the ability of the developed risk index to predict patient survival, it was compared to the most commonly used risk index in studies of dialysis patients – the Charlson Comorbidity Index (CCI). The CCI was originally developed to predict survival among general medical patients,[107] but has since been modified for use among dialysis patients.[106] Details on the calculation of the modified CCI score are given in Chapter 2 (Table 2.2.) and definitions of the variables used in the score are given in Appendix A.4.

Using the modified CCI to predict survival in the validation dataset gave a HR of 1.21 (95% CI 1.14, 1.28, p<0.0001) and c-statistic 0.63, which is significantly lower than that observed for the ATTOM risk index (0.72). The calibration slope was also much poorer (0.19, SE 0.03). Calibration-in-the-large could not be calculated as the equation for predicting survival from the modified CCI was not provided in the paper by Hemmelgarn et al.[106]

7.3.5. Listing status by ATTOM risk index

In the validation dataset, listing data were available for 1245 of 1246 patients. A total of 514 (41.3%) patients were activated on the transplant waiting list within 2 years of starting dialysis. Of these, 154 (30.0%) were listed prior to the start of dialysis. Table 7.9 and Figure 7.3 show the proportion of patients in the validation dataset who were listed within 2 years, stratified by ATTOM risk index quartile. This shows that lower risk index quartiles were associated with a higher rate of listing.

Table 7.9. 2 year listing rate by ATTOM risk index quartile

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
% listed	69.3	48.1	29.3	19.6

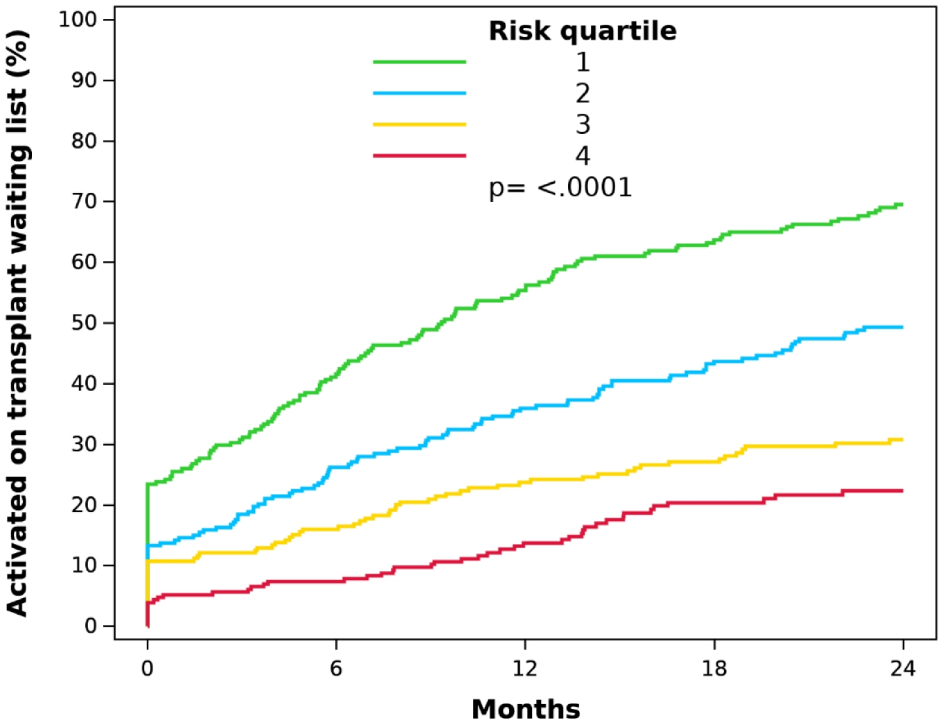

Figure 7.3. Cumulative incidence plot of listing within 2 years of starting dialysis by ATTOM risk index quartile**.** Patients who were listed prior to the start of dialysis were assigned a listing time of 0.

Surprisingly, 30.7% of the patients in risk quartile 1 and 51.9% of the patients in risk quartile 2 were not listed, despite having a high probability of surviving to 2 years (95.5% and 91.5% respectively, Figure 7.2). This was explored further by analysing the survival of patients in risk quartile 1 (Figure 7.4) and risk quartile 2 (Figure 7.5) stratified by listing status.

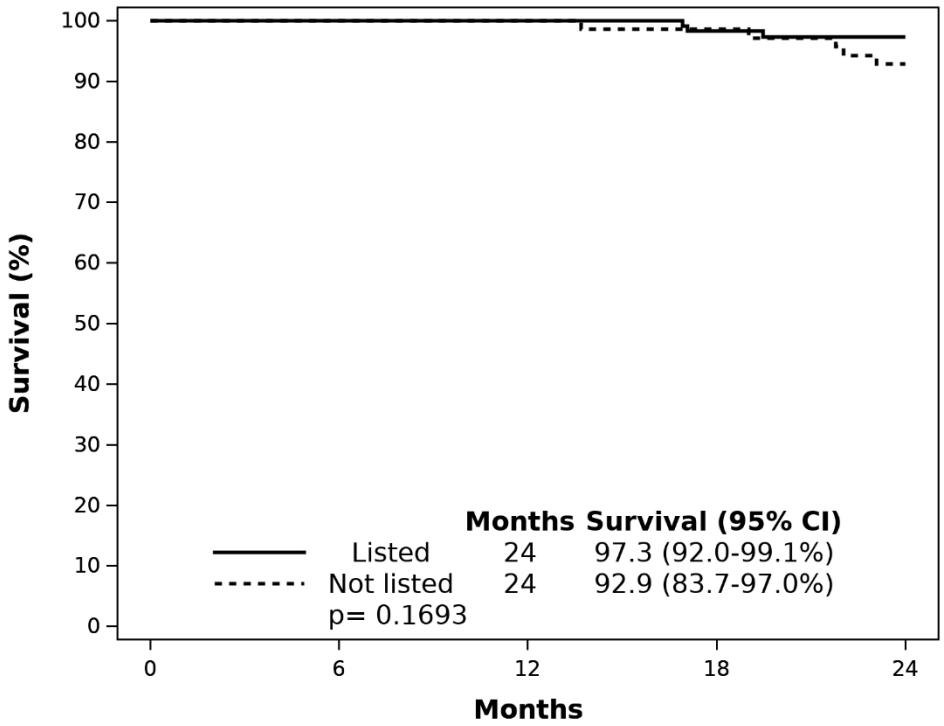

Figure 7.4. KM survival plot of risk quartile 1 patients stratified by listing status

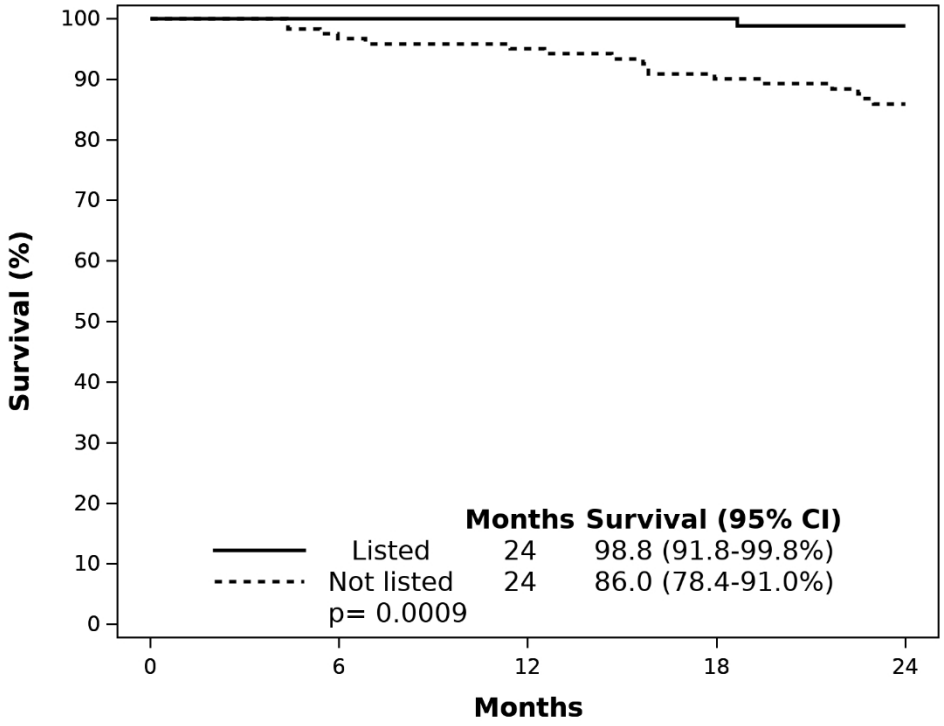

Figure 7.5. KM survival plot of risk quartile 2 patients stratified by listing status

Among the patients in risk quartile 1, there was no significant difference in survival between patients who were listed and patients who were not listed within 2 years of starting dialysis (p=0.169). Both groups experienced good survival at 2 years, thus suggesting that the 30.7% of patients in this quartile who were not listed, may represent a group of patients who are suitable for listing but may be experiencing barriers or inequity in access to transplantation. This is explored in more detail below. Among the patients in risk quartile 2, patients who were not listed (51.9%) did experience significantly worse survival compared to those who were listed (p=0.0009). This difference may be due to factors not included in the model, or it may be accounted for by the ability of clinicians to make an overall assessment of the patient's general fitness, which may not necessarily be quantifiable by specific factors. However the patients in risk quartile 2 who were not listed still experienced reasonable survival at 2 years (86%), and may also represent a group of patients who should be considered for transplant listing.

In order to explore the potential reasons for non-listing among the patients in risk quartile 1, a comparison of comorbidity (Table 7.10) and sociodemographic factors (Table 7.11) between listed and non-listed patients in this quartile was undertaken. This showed a significantly higher prevalence of ischaemic heart disease, mental illness and obesity among non-listed patients. Furthermore, significant sociodemographic barriers to listing were identified, including Black ethnicity, non car-ownership, non home-ownership, unemployment and not being able to work due to long term illness or disability.

Table 7.10. Comorbidity of listed and non-listed patients in risk quartile 1 of the validation dataset

Variable	Listed [n=160]	Not listed [n=71]	p-value
Diabetes	13 [8.1]	8 [11.3]	0.443
Ischaemic heart disease	2 [1.3]	6 [8.5]	0.006
Heart failure	1 [0.6]	3 [4.2]	0.053
Atrial fibrillation	0	0	.
Cardiac valve replacement	0	0	.
Pacemaker	1 [0.6]	1 [1.4]	0.553
Cerebrovascular disease	2 [1.3]	4 [5.6]	0.053
Peripheral vascular disease	1 [0.6]	1 [1.4]	0.553
Abdominal aortic aneurysm	0	0	.
Chronic respiratory disease	9 [5.6]	2 [2.8]	0.355
Chronic liver disease	0	0	.
Blood borne viruses	2 [1.3]	3 [4.2]	0.152
Malignancy	2 [1.3]	3 [4.2]	0.152
Mental illness	8 [5.0]	10 [14.1]	0.018
Dementia	0	0	.
BMI, kg/m^2			0.0005
Underweight (<18.5)	4 [2.5]	1 [1.4]	
Normal (18.5 - 24.9)	72 [45.0]	25 [35.2]	
Overweight (25.0 - 29.9)	50 [31.3]	11 [15.5]	
Obese (≥30.0)	34 [21.3]	34 [47.9]	

Data are number [%].

p-value is for chi-square test.

Table 7.11. Sociodemographic characteristics of listed and non-listed patients in risk quartile 1 of the validation dataset

Variable	Listed [n=160]	Not listed [n=71]	p-value
Age	42.8 [31.6 - 50.3]	45.0 [34.1 - 51.5]	0.524
Gender			0.252
Male	126 [78.8]	51 [71.8]	
Female	34 [21.3]	20 [28.2]	
Ethnicity			0.002
White	125 [79.1]	53 [75.7]	
Asian	16 [10.1]	1 [1.4]	
Black	13 [8.2]	16 [22.9]	
Other	4 [2.5]	0	
Car ownership	117 [76.5]	40 [58.0]	0.005
Home ownership	69 [45.1]	16 [23.2]	0.002
Qualifications			0.547
Higher education level	33 [21.6]	13 [18.8]	
Secondary education level	88 [57.5]	37 [53.6]	
No qualifications	32 [20.9]	19 [27.5]	
Employment status			<0.0001
Employed	85 [55.6]	11 [15.9]	
Unemployed	20 [13.1]	10 [14.5]	
Long term sick / disability	35 [22.9]	43 [62.3]	
Retired	4 [2.6]	1 [1.5]	
Other	6 [14.0]	3 [1.7]	

Data are median [IQR] or number [%].

Wilcoxon test for age, all others chi-square test.

7.4. Discussion

In this national prospective cohort study, we have created and internally validated a novel risk index for the prediction of 2 year survival on dialysis in the UK. Variables in the risk index included age, gender, diabetic nephropathy, serum albumin, heart failure, atrial fibrillation, chronic respiratory disease, chronic liver disease, malignancy and underweight BMI, as measured at the time of starting dialysis. The majority of the variables that were found to be important predictors of mortality in the risk index were comorbidities. This is unsurprising as the impact of comorbid disease on survival on dialysis is well established.[90-93, 310, 319-321] The additional negative impact of increasing age, low serum albumin and low BMI in the risk index is also consistent with the published literature.[93, 114, 322-326] The predictors that were used in the risk index are all readily available variables, and as such it could be easily implemented into routine clinical practice. The risk index is applicable to both HD and PD patients, in contrast to previous studies.[310, 311, 319]

We found that the ATTOM risk index had better performance characteristics compared with the frequently used CCI score. The CCI was originally developed in general medical patients in the US and subsequently adapted to predict survival in incident dialysis patients in Canada.[106] The marked international differences in survival on dialysis means that any risk scores developed using patients from other countries are unlikely to be applicable to UK dialysis patients,[114] and may account for the superior performance of the ATTOM risk index compared with the modified CCI. Two other studies to date have reported on the patient and comorbidity factors increasing

mortality among incident dialysis patients in the UK. Cherukuri et al. showed that several comorbidities in addition to older age and high calcium phosphate product were associated with overall mortality at 5 years. However, the study only performed univariable analyses, and was conducted in a single UK centre with a small number of patients (n=94), and as such the results do not have sufficient reliability or generalisability for the entire UK dialysis population.[327] Wagner et al. conducted a national multicentre study in the UK and developed a model for prediction of 3 year mortality on dialysis that included age, ethnicity, primary kidney disease, treatment modality, diabetes, cardiovascular disease, smoking, haemoglobin, serum albumin, creatinine and calcium.[92] The model reached a c-statistic of 0.73, which is very similar to the performance of the ATTOM risk index. However, the model was developed using UK renal registry data which only collects data on a limited number of comorbidities and is known to have a high level of missing data (particularly missing comorbidity data); this resulted in 50% of the study population being excluded. The ATTOM dataset benefits from good data completeness and the inclusion of data on an extensive range of comorbidities that were collected on a national basis in a prospective study, providing better reliability than registry data. Furthermore, the study by Wagner et al. was conducted using a more historical cohort of dialysis patients (2002-2004), and thus the risk index developed from our more contemporary cohort (2011-2013) is more applicable to current dialysis patients.

There are a number of ways in which the ATTOM risk index could be implemented into clinical practice. It can provide both patients and clinicians

with valuable quantifiable prognostic information, thereby enabling treatment decisions and planning to be tailored to individual patients. The model can also be utilised in future research targeted at patients with specific risk-profiles, or to provide adjustment for case-mix in clinical studies. For many patients with ESRD, dialysis is not the most effective renal replacement therapy, and the ultimate goal is for a better life expectancy and quality of life through the option of kidney transplantation.[7, 8, 10] However, the number of patients who actually achieve transplantation is greatly restricted by the vastly insufficient number of donor organs. In 2018 there were 5033 patients on the waiting list for a deceased donor kidney transplant in the UK. Although this number has begun to fall in recent years, this still equates to a lengthy median waiting time of 2 years.[13] Not being able to survive the wait is a real risk for many patients with ESRD. Between 2017-2018, 245 patients died whilst waiting for a kidney transplant and 439 patients were removed from the list (typically due to clinical deterioration resulting in becoming unsuitable for transplantation).[13] Moreover, it is well recognised that many ESRD patients experience inequity in access to transplantation or delayed referral for transplant assessment. Previous research has shown that various patient factors such as older age, non-White ethnicity and social deprivation, disadvantage patients in accessing transplantation.[3-5] Yet, perhaps the most concerning finding is that there is consistent evidence for significant variation in access to transplantation between centres in the UK, that cannot be explained by differences in patient factors or case-mix.[3-5, 315] Discrepancies in centres' assessment processes for determining patient suitability for transplantation and differences in clinicians' views towards patient selection are likely to be major contributing factors to the observed inconsistencies in

listing and transplantation across the UK.[6, 49] In this study, almost a third of patients with the greatest predicted survival (patients in risk quartile 1), were not listed for transplantation within 2 years. Non-listed patients were significantly more likely to have obesity, ischaemic heart disease or mental illness. It is likely that in many centres, patients who would otherwise have good predicted survival are being declined for transplant listing due to these factors. It is also clear that sociodemographic factors including ethnicity and social deprivation act as barriers to transplant listing in patients who have good predicted survival outcomes. The ATTOM risk index provides an objective and evidence-based means of predicting patient survival on dialysis. We propose that this tool could be used to inform a nationally agreed threshold at which patients are deemed to have a high likelihood of surviving a 2 year period on dialysis, and as such should be considered for referral for transplantation or activation on the waiting list. This would provide a transparent means of risk-stratification that ensures that those listed have a reasonable expectation of surviving the wait for transplantation. Furthermore, it would likely result in a reduction in the size of the waiting list, as well as greatly improved equity in access to transplantation across the UK. The proposed listing tool does however bring an important question to the fore; what is an acceptable survival probability at which patients should be considered for listing? Currently, the UK listing policy states that any condition with a predicted life expectancy of <2 years is an absolute contraindication to listing.[40] This is in line with European best practice guidelines that also that recommend exclusion of patients with a life expectancy of less than 2 years.[328] However, these guidelines do not give explicit details on the method that should be used to predict 2 year life

expectancy. In contrast, in New Zealand an estimated 5 year post-transplantation survival of over 80% is a requirement for entry to the waiting list.[329] Estimates are calculated from a survival prediction tool, based on an index derived and validated in a US dataset of 170 000 patients.[330] Patients are rescored annually or at the time of any change in their health status, and removed from the waiting list if their score falls below 70%.[331] While these criteria are relatively strict in comparison to UK and European guidelines, they do provide a clear, objective and standardised means of determining access to the waiting list. If a listing tool were to be adopted in the UK, the survival probability threshold for listing would need to be agreed on a national basis, with input from all stakeholders, including patients. The policy would also require continued re-evaluation and a robust and transparent framework of oversight. A similar concept is already in operation in the UK for liver transplantation. Access to the waiting list is based on predicted survival without a transplant, as estimated by the United Kingdom Model for End-Stage Liver Disease (UKELD) score.[332] Once on the waiting list, the organ offering scheme is based on a transplant benefit score i.e. the difference between the patient's predicted survival without a transplant and their predicted survival with a transplant from a given donor liver. The transplant benefit score is calculated using 21 recipient and 7 donor characteristics.[333] The patient with the greatest predicted survival benefit from a given donor liver is prioritised for that donor. With longer follow up of patients in the ATTOM study, it is anticipated that future analyses will be able to provide a similar scoring system for prediction of post kidney transplant survival.

There are a number of limitations to the study. First, we were unable to recruit the entire UK dialysis population, and as such the risk index may not be as reliable in certain patient groups who were underrepresented in the sample. This limitation was a compromise that was taken in order to be able to prospectively collect extensive and detailed data on a national sample of patients with good data completeness. We sought to reduce bias by including patients from all 72 renal units in the UK. Secondly, again for practical reasons, we were only able to collect data on risk factors at a single point in time (at the start of dialysis), and therefore were unable to assess the impact of the development of new risk factors or worsening of existing risk factors over time. Third, although the risk index performed well on internal validation, it requires further external validation in independent datasets to provide further information about the robustness of the model.

The ATTOM risk index uses a small number of readily available basic patient variables to provide prediction of 2 year survival on dialysis with good accuracy. Further research is required to externally validate the risk index and assess the feasibility of employing it as a criterion for access to the transplant waiting list.

CHAPTER 8

Conclusions

Like elsewhere in the world, kidney transplantation in the UK has seen incredible progress and development since its inception less than half a century ago. Kidney transplantation is now established as the optimal treatment strategy for ESRD due its superior survival benefits, quality of life and cost-effectiveness when compared with dialysis. The fact that survival rates from transplantation continue to improve year on year, despite the growing pressures on the NHS is a remarkable achievement and a testament to the relentless hard work and dedication of the transplant community. While there has been great success in increasing the number of donor organs and reducing the size of the waiting list in the UK, there is still a long way to go. The ongoing shortfall between supply and demand means that disparities in access to transplantation have become a major issue. This is particularly pronounced for certain disadvantaged groups in society. The incidence of patients requiring RRT in the UK continues to rise, alongside an increase in the age of the population and causal factors such as type 2 diabetes mellitus and hypertension.[334] Multimorbidity among potential transplant recipients has become increasingly common. This has resulted in uncertainty and variability across the UK in the evaluation of risk and benefit in the context of kidney transplantation.

There was limited research on these issues in the UK, and studies to date were generally retrospective or single centre analyses. Therefore, this thesis set out to address the concerns related to access to and outcomes from renal transplantation in the UK as part of a national prospective cohort study: Access to Transplantation and Transplant Outcome Measures (ATTOM). This

was the first study to include ESRD patients from all 72 renal units in the UK. The aims were to explore the following questions:

1) What factors may be contributing to inequity in access to transplantation in the UK?

2) How do patient factors including comorbidity affect graft and patient survival after renal transplantation, and do survival rates differ between centres in the UK?

3) Do patient reported outcome measures differ after living and deceased donor kidney transplantation?

4) What factors affect the survival of patients on dialysis, and can these risk factors be quantified in a survival prediction score aimed at reducing inequity and standardising access to the waiting list?

Each of these questions are discussed individually below.

1) What factors may be contributing to inequity in access to transplantation in the UK?

The study performed in Chapter 3 demonstrated significant differences in the comorbidity burden of listed and transplanted patients between centres in the UK. The findings suggest that some centres are listing and transplanting patients with significantly higher comorbidity than others, and thus centre

differences in selection criteria and assessment of risk may be contributing to inequity in access to transplantation in the UK.

Striking differences in patient factors between dialysis, waiting list and transplant patients were also highlighted in Chapter 3. The analysis showed that there were two levels at which patients are disadvantaged in accessing transplantation. Patients on dialysis were more likely to be older, have lower educational attainment and have greater socioeconomic deprivation compared with patients who made it to the waiting list or to transplantation. Interestingly, previously documented ethnicity differences at this level were not found in this study and may reflect an improvement in access to the waiting list for patients from ethnic minorities. Additional differences were noted between patients on the waiting list and those who achieved transplantation. Females, ethnic minorities, patients with lower educational attainment and greater socioeconomic deprivation were underrepresented in the transplant group compared with the waiting list group. As the national allocation system should not be affected by socioeconomic factors, this led us to explore whether the disparities could be explained by differences between patients undergoing DDKT and LDKT in Chapter 4.

In Chapter 4, older age, Black and Asian ethnicity, being divorced, separated, widowed or single, lower educational attainment and greater socioeconomic deprivation were found to significantly lower the likelihood of LDKT versus DDKT. Geographic factors were also identified as contributing to disparities in access to LDKT. We also investigated whether similar factors could act as barriers to pre-emptive transplantation. Asian ethnicity, unemployment and

greater socioeconomic deprivation were associated with a lower likelihood of pre-emptive LDKT versus LDKT after the initiation of dialysis. These findings demonstrate the strength of social factors in influencing access to transplantation. In the context of recent initiatives to increase the rate of LDKT in the UK, the results are important for identifying disadvantaged patient groups and developing targeted interventions. These results were presented to Parliament at the living donor transplant summit (22nd November 2017) hosted by the all-party parliamentary kidney group, as part of a manifesto to increase LDKT in the UK. Several interventions are now underway, using culturally sensitive and tailored home education programmes to target disadvantaged patient groups.

2) How do patient factors including comorbidity affect graft and patient survival after renal transplantation, and do survival rates differ between centres in the UK?

The analysis in Chapter 5 identified the key comorbid conditions that predict poorer two year graft and patient survival after kidney transplantation. Peripheral vascular disease and obesity were associated with a two- to three-fold increased risk of graft failure, while the risk of death was approximately doubled for cerebrovascular disease, tripled for heart failure and quadrupled for chronic liver disease. The study also yielded some interesting findings with regards to other patient factors. Previous US studies have shown that the negative effect of pre-transplant dialysis on survival outcomes after transplantation is evident after just 6 months on dialysis.[19] In this study, the detrimental effect of dialysis was only associated with poorer outcomes after a period of 3 years on dialysis. This may reflect the superior survival of

patients on dialysis in the UK compared with the US, as well as improvements dialysis care over time. The superior graft survival of LDKT over DDKT, was confirmed in the fully adjusted model accounting for significant comorbidity variables. The lack of difference in patient survival between LDKT and DDKT suggests that recipient variables including comorbidity may be more important for patient survival outcomes within 2 years than the type of donor. The risk associated with these important patient factors were quantified in this analysis and can be used to fully inform patients of their individual risks of transplantation, thereby facilitating shared decision-making and informed consent.

Contrary to previous registry reports, there was no evidence of inter-centre variation in the survival outcomes of transplant patients in the fully adjusted multivariable models. This work provides a strong argument for the inclusion of comorbidity factors in future registry analyses to avoid inappropriate labelling of centres as poor performers without adequate risk adjustment.

Due to the excellent survival outcomes of transplant recipients in the current era and the relatively short period of follow up of 2 years, there were insufficient events to allow development of a post-transplant survival risk score. At 5 years post-transplantation we plan to revisit this analysis, as the higher number of deaths and graft failures at this time point will allow splitting of the cohort into derivation and validation datasets for development of a risk index.

Part of the original research plan was to explore how patient factors and comorbidity affected the survival benefit of transplantation over dialysis in order to determine which patients would benefit most and which the least from transplantation. This was the reason for recruiting a matched control cohort of patients on the waiting list, as it would not have been appropriate to directly compare incident dialysis patients to incident transplant patients due to the bias introduced by the selection process for transplantation. However, we were unable to conduct this analysis as a significantly higher than expected proportion of the waiting list cohort (~50%) were transplanted within the 2 year follow up period. This reflects the increase in the number of donors and transplants and the decrease in the waiting list that happened over the follow up period of the study. During the planning of the study, the number of available donors was significantly lower and was static, and the waiting list had reached an all-time high. Therefore, we did not anticipate that such a high proportion of the waiting list cohort would be transplanted. After discussion with the statistics team at NHSBT, it was decided that we would be unable to conduct a robust analysis with the available data.

3) Do patient reported outcome measures differ after living and deceased donor kidney transplantation?

The study performed in Chapter 6 demonstrated significantly better patient reported health status, wellbeing, general quality of life, renal-dependent quality of life and renal treatment satisfaction for living versus deceased donor kidney transplantation at 1 year. The findings therefore enhance the recognised clinical benefits of LDKT and support the promotion of LDKT as the optimal form of transplantation. A concerning but understandable finding

of the study was that patients who underwent pre-emptive transplantation reported significantly worse treatment satisfaction than patients who received a period of dialysis prior to transplantation. This highlights the need for improved efforts to educate patients about the benefits of pre-emptive transplantation, to manage patient expectations and to provide psychological support throughout the whole treatment journey. Reassuringly, pre-emptive transplant recipients did not report inferior health status, psychological well-being and quality of life, compared with other transplant recipients.

4) What factors affect the survival of patients on dialysis, and can these risk factors be quantified in a survival prediction score aimed at reducing inequity and standardising access to the waiting list?

In Chapter 7, a comprehensive analysis of patients on dialysis showed that older age, female gender, lower serum albumin, being underweight or having diabetes, heart failure, atrial fibrillation, chronic respiratory disease, chronic liver disease or malignancy were important independent predictors of mortality within two years of starting dialysis. The results were developed into a novel survival prediction score that was internally validated, with good performance statistics. Further research is required to externally validate the score. The score could be easily implemented in the clinical setting to provide patients with individual survival prediction. We also propose that it could be used as a tool to aid listing decisions, thereby providing an objective and evidence based means of standardising access to the waiting list and improving equity of access to transplantation. However, the predicted survival probability at which patients should be considered for listing would

need to be agreed on a national basis with input from all relevant stakeholders, and most importantly patients.

The findings of this thesis have the ability to positively impact the care of patients with ESRD in the UK by driving initiatives to reduce inequity in access to transplantation, targeting disadvantaged patient groups, providing individual survival prediction for patients, informing national guidelines for fairer transplant listing and allocation and guiding future research into improving outcomes for all patients.

The work described in this thesis was part of the scientific evidence presented to and considered by a working group involved in the design of a new national kidney offering scheme in the UK. The terms of reference of the working group were to determine the criteria for listing for a kidney transplant, to evaluate the key principles of allocation, to consider whether priorities should differ at the extremes of age, to determine how best to maximise the benefit of each donor-recipient combination to include consideration of measures of organ quality and to determine the contribution of time spent on the waiting list to allocation priority. The recommendations from the working group were used in the development of the new national kidney offering scheme, which is currently being finalised.

Further work is required. A number of targeted interventions for improving access to transplantation are already underway in some pilot sites in the UK, and if successful could be rolled out across all centres. The importance of

comorbidity in the survival outcomes of ESRD patients has been highlighted in this work, and provides a case for exploring methods in which accurate comorbidity variables could be routinely collected by the UK transplant registry and UK renal registry. This would significantly enhance the national analyses produced by the registries and open up new insights into how the outcomes of ESRD patients could be further improved. Further research is needed to determine whether optimisation of specific comorbidity risk factors can improve survival outcomes. The patients enrolled in the study will continue to be followed up so that longer term outcomes can be analysed. We plan to update our analyses at 5 and 10 years. In addition to the risk index for dialysis patients, a risk index for post-transplant survival will be explored. Additional work is required to investigate whether interventions can improve the patient reported outcomes of transplant recipients, particularly DDKT recipients. We also intend to take forward the work done on the survival prediction score for patients on dialysis, by incorporating it into a user friendly mobile app tool, and assessing ways in which it could be integrated into the listing process in the UK.

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APPENDIX

A.1. ATTOM steering group members

Name and Affiliation	Role
Dr Rishi Pruthi University of Southampton	Workstream 1 researcher
Dr Dominic Taylor University of Southampton	Workstream 1 researcher
Dr Rommel Ravanan Richard Bright Renal Unit, Southmead Hospital, Bristol	Workstream 1 lead, nephrologist
Dr Diana Wu University of Edinburgh	Workstream 2 researcher
Mr Gabriel Oniscu Transplant Unit, Royal Infirmary of Edinburgh	Workstream 2 lead, transplant surgeon
Prof John Forsythe Transplant Unit, Royal Infirmary of Edinburgh, NHS Blood and Transplant, Bristol	Workstream 2 co-lead, transplant surgeon
Dr Andrea Gibbons Health Psychology Research Unit, Royal Holloway University of London, Egham	Workstream 3 researcher
Dr Melania Calestani University of Southampton	Workstream 3 researcher
Prof Clare Bradley Health Psychology Research Unit, Royal Holloway University of London, Egham	Workstream 3 lead, health psychologist
Miss Bernadette Li Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine	Workstream 4 researcher
Prof John Cairns Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine	Workstream 4 lead, health psychologist
Prof Andrew Bradley Department of Surgery, Addenbrooke's Hospital, Cambridge	Chair, transplant surgeon
Prof Chris Watson Department of Surgery, Addenbrooke's Hospital, Cambridge	Transplant surgeon
Dr Charles Tomson Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne	Nephrologist
Dr Christopher Dudley Richard Bright Renal Unit, Southmead Hospital, Bristol	Nephrologist
Dr Damian Fogarty	Nephrologist, UKRR advisor

Belfast Health and Social Care Trust, UK Renal Registry	
Dr Wendy Metcalfe Transplant Unit, Royal Infirmary of Edinburgh	Nephrologist, SRR advisor
Prof Paul Roderick University of Southampton	Epidemiologist
Prof Heather Draper University of Warwick	Bioethicist
Mrs Rachel Johnson NHS Blood and Transplant, Bristol	Statistician
Mrs Lisa Mumford NHS Blood and Transplant, Bristol	Statistician
Mr Matthew Robb NHS Blood and Transplant, Bristol	Statistician
Dr David Ansell UK Renal Registry	UKRR advisor
Mr Timothy Statham National Kidney Federation	Patient representative
Mrs Lesley Ross	Patient representative
Mrs Michelle Satchwell	Patient representative

A.2. Data proforma

Demographic variables – collected for all patients

Variable	Options
Date of data entry	
Cohort	Incident dialysis Incident transplant Matched control
Hospital number	
Post code	
Transplant centre	
Renal unit	
Date of Birth	
Gender	Male Female
Ethnicity	White Black Asian Other
Date first seen by nephrologist	

Socioeconomic variables – collected for all patients

Variable	Options
Civil status	Single Married Living with partner Separated Divorced Widowed
Highest qualification	No qualifications Secondary education level Higher education level
Employment status	Employed Unemployed Long term sick/disabled Retired Other
Car ownership	No

	Yes
Number of vehicles	
Home ownership	No Yes
Number of dependents	
Heath literacy: how often do you need help to read instructions, leaflets or other written material from your doctor or pharmacy?	Never Rarely Sometimes Often Always
First language	
If not English, please rate your fluency in English	Basic Moderate Good
Were you born in the UK?	No Yes

Clinical variables – collected for all patients

Variable	**Options**
Primary renal disease	Diabetic nephropathy Glomerulonephritis Polycystic kidney disease Pyelonephritis Hypertensive nephropathy Renal vascular disease Uncertain Other: (free text)
Diabetes	No Yes: Type 1 Type 2
Ischaemic heart disease	No Yes: Angina NSTEMI STEMI PCI Coronary artery bypass graft operation
Heart Failure	No Yes

Atrial fibrillation	No Yes
Cardiac valve replacement	No Yes: Aortic Mitral Tricuspid Pulmonary
Permanent pace-maker	No Yes
Cerebrovascular disease	No Yes: TIA CVA / Stroke Carotid intervention
Peripheral vascular disease	No Yes: Claudication Radiological or surgical intervention Amputation
Abdominal aortic aneurysm	No Yes: Surveillance Radiological or surgical repair
Chronic respiratory disease	No Yes: Asthma COPD Bronchiectasis
Chronic liver disease	No Yes: Cirrhotic Non-cirrhotic
Blood borne viruses	No Yes: Hepatitis C Hepatitis B HIV
Malignancy	No Yes: (free text)
Mental illness	No Yes
Dementia	No

	Yes
Other diagnosis	(free text)
Height (cm)	
Dry weight (kg)	
BMI (kg/m²)	
Smoking status	No Yes Ex-smoker
Number of cigarettes per day	
Previous transplant	No Yes
Number of previous transplants	

Dialysis variables – collected for incident dialysis cohort

Variable	**Options**
Start of dialysis date	
Type of dialysis	Haemodialysis Haemodiafiltration Continuous ambulatory peritoneal dialysis Automated peritoneal dialysis
Type of dialysis access	Arteriovenous fistula Arteriovenous graft Tunnelled line Non-tunnelled line

Transplant variables – collected for incident transplant cohort

Variable	**Options**
Date of transplant	
Type of transplant	Kidney only Kidney + pancreas Kidney + other organ
Donor type	Living DBD DCD
If living donor, relationship	Parent Child Sibling

	Other blood relative Spouse/partner Pooled/altruistic Other non-related
Pre-transplant treatment modality	Pre-emptive Haemodialysis Haemodiafiltration Continuous ambulatory peritoneal dialysis Automated peritoneal dialysis Failing transplant
Start of dialysis date	
Type of dialysis access	Arteriovenous fistula Arteriovenous graft Tunnelled line Non-tunnelled line
Date of activation on waiting list	
Recipient calculated reaction frequency (%)	
Recipient blood group	A B AB O
HLA mismatch group	1 2 3 4
Cold ischaemic time	
Donor age	
Donor sex	Male Female
Donor ethnicity	White Black Asian Other
Donor blood group	A B O AB
Donor height (cm)	
Donor weight (kg)	
Donor BMI (kg/m²)	
Donor cause of death	Cardiac

	CVA Respiratory Trauma Infection Malignancy Other
Donor hypertension	No Yes
Donor diabetes	No Yes
Donor creatinine	
Donor CMV	Negative Positive Result awaited Not tested

Waiting list variables – collected for waiting list cohort

Variable	**Options**
Date of activation on waiting list	
Type of transplant listed for	Kidney only Kidney + pancreas Kidney + other organ
Treatment modality at time of data collection	Pre-emptive Haemodialysis Haemodiafiltration Continuous ambulatory peritoneal dialysis Automated peritoneal dialysis Failing transplant
Start of dialysis date	
Type of dialysis access	Arteriovenous fistula Arteriovenous graft Tunnelled line Non-tunnelled line

Investigations – collected for incident transplant and waiting list cohorts

Variable	**Options**
Cardiac Investigations	None

	Echo Treadmill test MPI / nuclear scan Stress echo Coronary angiogram CT coronary angiogram
Pulmonary Function Tests	No Yes
Vascular Investigations	None Doppler lower limbs Doppler carotid Doppler both CT angiography Conventional angiography

A.3. Variable definitions

Ethnicity

White – British, Irish, European, other White background
Black – Caribbean, African, other Black background
Asian – Indian, Pakistani, Bangladeshi, Indian subcontinent, other Asian background
Other – Any other background including Chinese and mixed backgrounds

Highest qualification

No qualifications
Secondary education level – Ordinary level (O-level), General Certificate of Secondary Education (GSCE), General Certificate of Education Advanced level (A-level), National Vocational Qualification (NVQ) 1-3
Higher education level – Bachelor's Degree (e.g. BA/BSc), Higher Degree (e.g. MSc/PhD), NVQ 4-5

Employment status

Employed – full-time and part-time included
Unemployed
Long term sick/ disabled
Retired
Other – looking after the family home, not in work for some other reason, students

Primary renal diagnosis

Coded as per UK renal registry definitions (which are based on ERA-EDTA definitions). These can be found at: https://www.renalreg.org/wp-content/uploads/2018/06/19-AppH.pdf

Diabetes

Any cause of diabetes
Type I diabetes – Insulin required from time of diagnosis
Type II diabetes – Treatment with diet-control, oral antidiabetic medication or insulin

Ischaemic heart disease

Angina – chest pain on exertion, relieved by rest / GTN. As reported by patient or as documented on case notes with or without ECG changes, exercise tolerance testing or other imaging
NSTEMI – troponin rise and non-ST segment elevation ischaemic ECG changes such as ST depression, T-wave inversion or no ECG changes.
STEMI – troponin rise and ST segment elevation on ECG
PCI – coronary angioplasty with or without stent insertion
CABG – coronary artery bypass graft operation

Heart failure

Includes any of the following:
Congestive cardiac failure
Left ventricular failure
Right ventricular failure
Left or right ventricular dysfunction on cardiac echo
Ejection fraction <30% on cardiac echo

Atrial fibrillation

Only includes patients in chronic atrial fibrillation at the time of recruitment, previous isolated episodes not included

Cardiac valve replacement

Any kind of cardiac valve replacement or repair

Permanent pacemaker

Currently has permanent pacemaker in situ

Cerebrovascular disease

Transient Ischaemic Attack (TIA) – also known as "mini-stroke". Transient episode of neurologic dysfunction caused by ischaemia without infarction. Symptoms typically lasting less than 24 hours
Cerebrovascular accident (CVA) – includes Ischaemic stroke, cerebral haemorrhage, subarachnoid haemorrhage or subdural haemorrhage confirmed on imaging
Carotid intervention – includes carotid endarterectomy and carotid angioplasty

Peripheral vascular disease

Claudication – lower limb pain on walking as reported by the patient, with or without doppler or angiographic evidence
Radiological or surgical intervention – includes angioplasty, endarterectomy, bypass graft
Amputation – amputation of any part of the limb

Abdominal aortic aneurysm

Surveillance – radiological diagnosis under surveillance
Radiological or surgical repair – previous endovascular or open surgical repair

Chronic respiratory disease

Asthma – inflammatory condition of the lungs causing recurrent attacks of breathlessness and wheezing, differs in severity and occurs in all age groups
Chronic obstructive pulmonary disease (COPD) – chronic and progressive airflow obstruction that is not fully reversible. FEV1/FVC ratio <0.7 and FEV1 $<$ 80% predicted
Bronchiectasis – abnormal and irreversible dilatation of the bronchi due to destruction of elastic and muscular tissue by acute or chronic inflammation and infection. Results in chronic infections and airway obstruction

Chronic liver disease

Persistent enzyme evidence of hepatic dysfunction with imaging or biopsy evidence of cirrhotic or non-cirrhotic liver disease

Blood borne viruses

Evidence of Hepatitis C or B or HIV PCR or antibody positive results

Malignancy

Diagnosis of any malignancy in the past or in the present. Does not include benign tumours such as breast adenoma, colon polyp, actinic keratosis etc.

Mental illness

Includes any kind of mental illness such as depression, psychosis, bipolar disorder, substance abuse, deliberate self-harm, schizophrenia

Dementia

Any form of dementia including vascular dementia and Alzhemier's disease

Type of dialysis

If the patient has been on more than one type of dialysis, this is the modality that the patient has spent most time on

Recipient calculated reaction frequency (cRF)

The cRF is a measure of recipient HLA sensitisation and is calculated as the percentage of 10,000 recent donors to which the recipient has pre-formed HLA antibodies

HLA mismatch group

HLA mismatches were classified into 4 levels as defined by the current UK deceased donor kidney allocation scheme: level 1 (000 HLA-A, B, DR MM), level 2 (0DR + 0/1B MM), level 3 (0DR + 2B MM) or (1DR + 0/1B MM) and level 4 (1DR + 2B MM) or (2DR MM)

Appendix A.4. Modified Charlson Comorbidity Index definitions

Myocardial infarction
ATTOM ischaemic heart disease variable = NSTEMI or STEMI

Congestive heart failure
ATTOM heart failure variable = YES

Peripheral vascular disease
ATTOM peripheral vascular disease variable = YES (all options included)
ATTOM abdominal aortic aneurysm variable = RADIOLOGICAL OR SURGICAL REPAIR

Cerebrovascular disease
ATTOM cerebrovascular disease variable = YES (all options included)

Dementia
ATTOM dementia variable = YES

Chronic pulmonary disease
ATTOM chronic respiratory disease = YES (all options included)

Diabetes without complications
ATTOM diabetes variable = YES
(ATTOM primary renal disease variable ≠ DIABETIC NEPHROPATHY)

Diabetes with complications
ATTOM primary renal disease variable = DIABETIC NEPHROPATHY

Moderate-severe liver disease
ATTOM chronic liver disease variable = CIRRHOTIC

Leukaemia
ATTOM malignancy variable = LEUKAEMIA, MYELOGENOUS LEUKAEMIA, LYMPHOCYTIC LEUKAEMIA, POLYCYTHEMIA VERA

Lymphoma

ATTOM malignancy variable = LYMPHOMA, HODGKIN'S, LYMPHOSARCOMA, WALDENSTROMS MACROGLOBULINAEMIA, MYELOMA, NON-HODGKIN'S

Metastatic disease

ATTOM malignancy variable = METASTATIC, METASTASES, METS

A.5. PROMs questionnaires

Questionnaire	Description	Range of possible scores

EuroQol five dimensions (EQ-5D-5L)	• General health status
	• 5 dimensions of health (today):
	  ○ Mobility
	  ○ Self-care
	  ○ Usual activities
	  ○ Pain / Discomfort
	  ○ Anxiety / Depression
	• Rated on 5 levels
	  ○ No problems
	  ○ Slight problems
	  ○ Moderate problems
	  ○ Severe problems
	  ○ Extreme problems
	• Converted to weighted index score using the value set for England*
	• Higher score indicates better health status
		-0.281 to +1.00

EuroQol visual analogue scale	• General health status • Rating of health (today) on visual analogue scale • 0 = worst health you can imagine • 100 = best health you can imagine	0 to 100

12-Item Well-Being Questionnaire (W-BQ12)	• General well-being
	• Calculated by combining scores from 3 subscales (12 items)
	  ○ Negative well-being
	  ○ Energy
	  ○ Positive well-being
	• Higher score indicates greater well-being
		0 to 36

General QoL (from RDQoL questionnaire)	• General QoL • Single item question rated from -3 (extremely bad) to +3 (excellent)	-3 to +3
Renal-dependent QoL (RDQoL)	• 17 aspects of life • Rating of impact of renal condition	-9 to +3

	• Rating of importance of each aspect of life • Combined to give an average weighted impact score • From −9 (most negative impact) to +3 (most positive impact)	
Renal treatment satisfaction questionnaire status version (RTSQs)	• Satisfaction with current renal treatment • Rated from 6 (very satisfied) to 0 (very dissatisfied) on 13 items • Higher score indicates greater satisfaction	0 to 78
Renal treatment satisfaction questionnaire change version (RTSQc)	• Satisfaction with current renal treatment compared with satisfaction with previous renal treatment • Rated from +3 (much more satisfied now) to −3 (much less satisfied now) on 13 items • Higher score indicates greater satisfaction with current compared with previous treatment	−39 to +39

* Devlin N, Shah K, Feng Y, Mulhern B, Van Hout B. Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. London: Office of Health Economics, January 2016. Available from https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england.

A.6. UK transplant centres and referring renal units

Belfast City Hospital
Altnagelvin Hospital
Antrim Hospital
Daisy Hill Hospital
Tyrone County Hospital
Ulster Hospital
Birmingham Queen Elizabeth Hospital
Heartlands Hospital
Russells Hall Hospital, Dudley
New Cross Hospital, Wolverhampton
Royal Shrewsbury Hospital
North Staffordshire – Stoke
Bristol Southmead Hospital
Gloucester Royal Hospital
RD&E Exeter
Dorset County Hosp
Cambridge Addenbrookes Hospital
Colchester
Ipswich Hospital
Lister Hospital, Stevenage
Norfolk & Norwich University Hospital
University Hospital of Wales, Cardiff
Morriston Hospital, Swansea
Walsgrave Hospital, Coventry
Royal Infirmary of Edinburgh
Aberdeen Royal Infirmary
Ninewells Hospital, Dundee
Queen Margaret's Hospital, Dunfermline
Raigmore Hospital, Inverness
Glasgow Western Infirmary
Crosshouse Hospital, Kilmarnock
Dumfries & Galloway Royal Infirmary
Monklands Hospital, Airdrie
St James's University Hospital, Leeds
Hull Royal Infirmary
St Lukes Hospital, Bradford
York District General Hospital
Leicester General Hospital
Royal Liverpool University Hospital
Arrowe Park Hospital, Wirral

University Hospital Aintree
Wrexham Maelor Hospital
Ysbyty Glan Clwyd, Rhyl
Ysbyty Gwynedd, Bangor
Bart's and the London Hospital, London
Basildon Hospital
Broomfield Hospital, Chelmsford
Southend
Guy's and St Thomas's Hospital, London
Kent & Canterbury Hospital
King's College Hospital
Royal Free Hospital, London
St George's Hospital, London
Royal Sussex County Hospital, Brighton
St Helier Hospital, Carshalton
West London Renal and Transplant Centre, London
Royal Infirmary, Manchester
Hope Hospital, Salford
Royal Preston Hospital
Freeman Hospital, Newcastle-upon-Tyne
Cumberland Infirmary, Carlisle
James Cook University Hospital, Middlesbrough
Sunderland Royal Hospital
Nottingham City Hospital
Royal Derby Hospital
Oxford Radcliffe Hospital
Royal Berkshire Hospital, Reading
Derriford Hospital, Plymouth
Royal Cornwall Hospital Treliske, Truro
Queen Alexandra Hospital, Portsmouth
Northern General Hospital, Sheffield
Doncaster Royal Infirmary

*Transplant centres are in bold type

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Global trends and challenges in deceased donor kidney allocation

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Worldwide, the number of patients able to benefit from kidney transplantation is greatly restricted by the severe shortage of deceased donor organs. Allocation of this scarce resource is increasingly challenging and complex. Striking an acceptable balance between efficient use of (utility) and fair access to (equity) the limited supply of donated kidneys raises controversial but important debates at ethical, medical, and social levels. There is no international consensus on the recipient and donor factors that should be considered in the kidney allocation process. There is a general trend toward a reduction in the influence of human leukocyte antigen mismatch and an increase in the importance of other factors shown to affect posttransplant outcomes, such as cold ischemia, duration of dialysis, donor and recipient age, and comorbidity. Increased consideration of equity has led to improved access to transplantation for disadvantaged patient groups. There has been an overall improvement in the transparency and accountability of allocation policies. Novel and contentious approaches in kidney allocation include the use of survival prediction scores as a criterion for accessing the waiting list and at the point of organ offering with matching of predicted graft and recipient survival. This review compares the diverse international approaches to deceased donor kidney allocation and their evolution over the last decade.

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The superior outcomes of kidney transplantation over dialysis and the growing incidence of end-stage renal disease have led to an exponential increase in the need for kidney transplantation worldwide.[1] In contrast, the number of deceased donors has changed little and is vastly insufficient.[2] Consequently, patients face longer waiting times, as well as a higher risk for morbidity and mortality while on the waiting list. In the US alone, the number of patients on the waiting list has doubled over the past decade, reaching around 100,000 patients, median waiting time has increased to over 4.5 years, and nearly 5000 patients die while waiting for a deceased donor kidney transplant every year.[3] Similar trends have been noted in other countries (Figure 1 and Table 1).

While living donors usually donate to a specified recipient, in most countries, deceased organ donation is non-directed and organs are offered to patients on a waiting list via an allocation scheme. Allocation schemes are generally governed by appointed transplant organizations that may operate at a regional, national, or even international level. Ownership of deceased donor organs is a controversial matter; in some countries, they are considered a national resource, whereas in others, they are retained within the donor region, and sharing among regions may be limited to payback requirements. Thus, allocation schemes vary from simple local programs to complex national algorithms. Furthermore, there is no universal consensus on the factors that should be considered in the allocation process, leading to considerable variation in the way patients are prioritized within different schemes.

The major debate in the allocation of scarce donor organs centers on the competing ethical values of utility (maximum outcomes) and equity (fairness). Consideration must be given to the efficient use of organs to optimize outcomes and the overall benefits to society, as well as to the welfare of individual patients and fair access to transplantation.[4] Utility-based allocation prioritizes patients with the best chance of a favorable outcome, aiming to achieve the maximum benefit from every transplanted organ. Inevitably, this gives rise to a debate over how benefit should be measured, that is whether by graft survival, patient survival, life years gained from transplant, or quality of life. Furthermore, it disadvantages patients who are less likely to experience a good outcome, such as those who are older, have diabetes, have more comorbidity, or have been on dialysis for a longer period of time.[5–9] Although an increasing

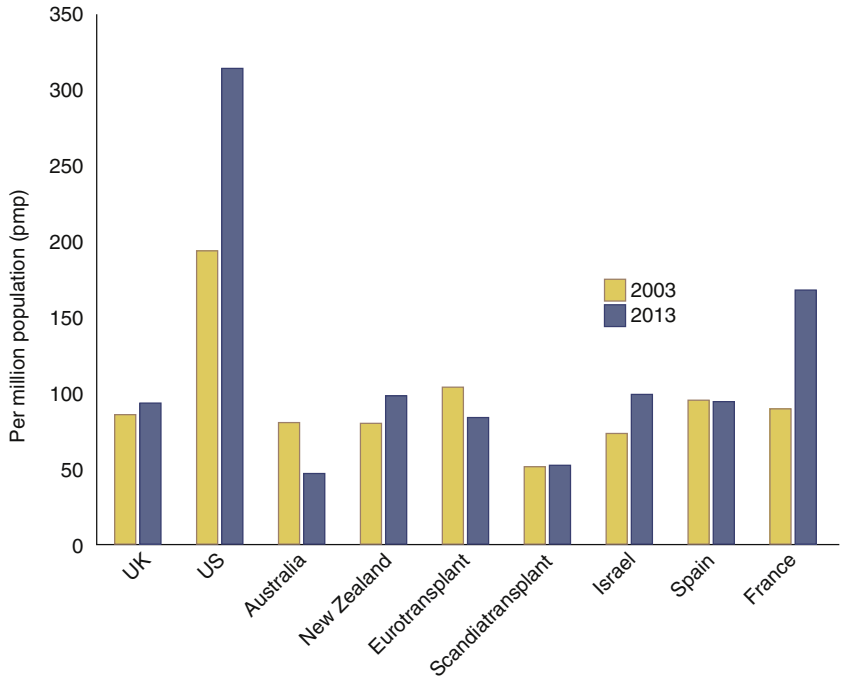

Figure 1 | Patients on kidney transplant waiting list 2003 versus 2013. Eurotransplant 2003: Austria, Belgium, Germany, the Netherlands, Luxembourg, and Slovenia. Eurotransplant 2013: Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Luxembourg, and Slovenia. Scandiatransplant: Denmark, Finland, Iceland, Norway, and Sweden. Data sources: UK,[87–89] US,[3,90,91] Australia,[92,93] New Zealand,[92,93] Eurotransplant,[94,95] Scandiatransplant,[96,97] Israel,[98,99] Spain,[98,99] and France.[98–100] Population data from United Nations. Department of Economic and Social Affairs Population Division. World Population Prospects: The 2015 Revision. Total Population – Both Sexes. Available at: https://esa.un.org/unpd/wpp/Download/Standard/Population/. Accessed April 11, 2016.

proportion of patients on the waiting list fall into the above categories, they still derive a significant survival benefit from transplantation.[1,10–12] The principle of equity necessitates fairness in organ allocation; however, this may be interpreted in various ways. Equity is commonly conceived as "equal opportunity," that is, every person who may benefit from a transplant should have an equal opportunity of receiving one.[13] It is important not to misinterpret this as equality; although equality involves treating all patients exactly the same (i.e., allocation by lottery), it neglects the fact that patients do not start from equal circumstances.[14] The discovery of human leukocyte antigen (HLA) matching as a major determinant of graft survival led to its principal role in the first formal allocation schemes.[15–17] However, it became apparent that such schemes resulted in inequitable access to transplantation for difficult-to-match patients.[18–20] Consequently, most schemes now award extra priority to highly sensitized patients and patients with rare HLA types (most commonly from ethnic minorities) who are biologically disadvantaged in finding a compatible donor, to equalize their opportunity for transplantation. "Queuing" (first come, first served) is another concept of equity that has been widely accepted in kidney allocation. However, with the increasing age and morbidity of patients on the waiting list, this approach has been challenged for favoring those who are able to survive the ever-increasing wait. Furthermore, with growing evidence for disparities in access to the waiting list, many schemes now measure the waiting time from the start date of dialysis as opposed to the listing date, although some countries are yet to adopt this approach. Priority for pediatric patients is universally acknowledged in view of the detrimental impact of renal failure and prolonged dialysis on growth and development (although the age cutoff and priority level substantially varies among different schemes). In contrast, the prioritization of younger adults over older ones is widely disputed. While advocates of the "fair innings" concept believe that equity should be measured by the opportunity to reach a normal life expectancy, critics argue that preferential allocation to younger patients is age discrimination.[21] The "prudential lifespan" provides an alternative concept of equity through the allocation of kidneys by age matching. This justifies the allocation of younger (and therefore "higher quality" kidneys) to younger recipients and the allocation of older kidneys to older recipients because all patients are treated similarly at a particular stage of life.[22] However, this approach becomes problematic if there is a discrepancy in the age distribution of donor and recipient pools. Moreover, age is just one of the many factors that influence the outcome of transplanted kidneys. A range of survival predictors are utilized in the emerging concept of longevity matching, where kidneys are allocated on the basis of matching estimated graft and recipient survival. This approach remains controversial, reflecting the enduring difficulties in achieving an acceptable balance between utility and equity.

This review compares the allocation schemes of several different countries and explores their evolution over the last decade.

United Kingdom

The first UK national kidney allocation scheme was a simple HLA-matching scheme that was introduced in 1989.[23] One kidney from each donor was allocated nationally to a "beneficially mismatched recipient" (defined as HLA-A, -B, and -DR mismatch 000, 100, or 010), whereas the paired donor kidney was allocated locally according to individual center policies.[17,23]

A revised scheme was implemented in 1998, after 3 distinct tiers of HLA mismatch were identified as major influences on graft outcome.[24] Allocation was prioritized on a national basis for tier 1 (000 mismatch) followed by tier 2 (100, 010, and 110 mismatch) patients; allocation was on a local basis for tier 3 patients (all other HLA-mismatch grades). Within tiers 1 and 2, priority was given to pediatric patients (<18 years), patients disadvantaged in finding a compatible donor (who are highly sensitized [panel reactive antibody, {PRA} ≥85%], are HLA-DR homozygous, or have blood group B), and local patients. A points score differentiated equally eligible patients within the tiers on the basis of recipient's age, donor-recipient age difference, waiting time (from listing date), matchability score, sensitization level, and balance of organ exchange among centers. Matchability was a measure of the likelihood of being offered a well-matched kidney (tier 1 or 2), with the aim being to improve access for difficult-to-match patients. However, because the points score was employed to only differentiate among equally HLA-matched patients, the overall effect of the point-scoring factors proved to be minimal. Although the 1998 scheme improved the level of HLA matching of allocated kidneys, the inequity of access remained a significant issue.[24]

In 2006, a new scheme was implemented, and this remains in place to date, albeit with minor modifications.[25] Previously deemed non-favorable levels of HLA mismatch were shown to achieve good outcomes; therefore, the new scheme places less emphasis on HLA matching, and except for zero HLA mismatches, HLA-A matching is no longer considered.[8] Zero HLA-mismatched patients retain top priority along with well-matched (100, 010, and 110) pediatric patients, HLA-DR homozygous patients, and highly sensitized patients (now measured as calculated reaction frequency, ≥85%). The calculated reaction frequency is the percentage of 10,000 recent donors to which the patient has pre-formed antibodies. The points score was also revised; where previously waiting time contributed the least points, it now has potentially the greatest influence (although it continues to be defined as the time from listing). Points for the recipient's age are combined with HLA mismatch in a novel approach to prioritize younger patients for well-matched grafts. This minimizes HLA sensitization and improves the likelihood of retransplantation, which is particularly crucial for younger recipients who are likely to require more than 1 graft in their lifetime. Other point-scoring factors include the proximity of the donor to the recipient center (to minimize ischemia), donor-recipient age difference, HLA-DR and -B homozygosity and blood group (to address imbalances of distribution between donor and recipient pools). Because the matchability score proved to be unsuccessful in improving equity, the 2006 scheme utilizes a different approach whereby rare HLA types are defaulted to more common related HLA types against which cross-reacting antibodies seldom form. In September 2014, the national scheme was extended to include allocation from donors after circulatory death. In the phase-in period, this allocation is only applicable to one kidney from donors after circulatory death who are aged 5 to 50 years.[26]

The 2006 scheme has successfully increased the number of transplants for highly sensitized, long-waiting, difficult-to-match and Black, Asian, and minority ethnic patients, without compromising graft or patient survival (Table 2). Nevertheless, the past decade has also seen an overall increase in the size of the waiting list, median waiting time (Table 1), and number of discarded kidneys.[27] This raises concerns regarding the efficiency and suitability of the allocation system within the context of an older and higher risk population of donors and recipients.

United States

The first US kidney allocation scheme was introduced in 1987, and a completely revised scheme was implemented for the first time in 2014.[28] Under the former system, the country was divided into 58 donor service areas (DSAs), responsible for local procurement and allocation of deceased donor organs.[29] Although there was mandatory national sharing of zero HLA-mismatched kidneys, these were required to be paid back to the procuring DSA. The large majority of organs were retained within and allocated by individual DSAs. Given that local organ supply relative to the demand varied widely among DSAs, substantial disparities were observed in the waiting time across the country.[30] In March 2000, the Department of Health and Human Services issued "The Final Rule" to establish a national framework for organ allocation and to reduce geographical inequities.[31] Following this, all kidneys were allocated via one of 4 sequences, according to the category of the donor:

- Standard criteria donors <35 years
- Standard criteria donors ≥35 years
- Expanded criteria donors (ECD)
- Donors after circulatory death

ECD kidneys were defined by an estimated risk for graft failure of ≥70% higher than standard criteria donor kidneys and were offered to specifically consenting recipients.[32] Within each sequence, priority was given to zero HLA-mismatched patients, blood group-identical patients, highly sensitized patients (calculated PRA, ≥80%), pediatric patients (<18 years), prior live organ donors, local patients, and DSAs owed a payback. A points score was used to rank individual patients (recipients of ECD or donor after circulatory death kidneys were ranked by waiting time only).[33] The points score was extensively modified over time toward fewer points for HLA matching (except for zero HLA mismatches, HLA-A matching was eliminated in 1995 and HLA-B matching was eliminated in 2003) and more points for

Table 1 | Kidney transplant and waiting list figures 2003 versus 2013

	UK		US		Australia		New Zealand	
Year	2003	2013	2003	2013	2003	2013	2003	2013
Population (million)[c]	59.5	64.0	291.0	317.1	19.7	23.3	4.0	4.5
Total kidney transplants								
n	1836	3256	15138	16895	543	882	111	115
pmp	30.9	50.9	52	53.3	27.6	37.9	27.8	25.6
DD transplants								
n	1386	2142	8668	11163	325	630	67	57
pmp	23.3	33.5	29.8	35.2	16.5	27	16.8	12.7
LD transplants								
n	450	1114	6470	5732	218	252	44	58
pmp	7.6	17.4	22.2	18.1	11.2	10.8	11	12.9
Patients on waiting list at year end								
n	5074	5881[d]	56514	99253	1591	1056	318	438
pmp	85.3	91.9	194.2	313	80.8	45.3	79.5	97.3
Died on waiting list								
n	298	279	3895	4644	45	3	x	x
pmp	5	4.4	13.4	14.6	2.3	0.1	x	x
Median waiting time, yr	2.3	2.7	3.2	4.5	3.7	2.7	x	x

DD, deceased donor; LD, living donor; pmp, per million population; x, data not available.
[a]Eurotransplant 2003: Austria, Belgium, Germany, the Netherlands, Luxembourg and Slovenia. Eurotransplant 2013 = Austria, Belgium, Croatia, Germany, Hungary, the Netherlands, Luxembourg, and Slovenia.
[b]Scandiatransplant: Denmark, Finland, Iceland, Norway, and Sweden.
[c]Data from United Nations. Department of Economic and Social Affairs Population Division. World Population Prospects: The 2015 Revision. Total Population – Both Sexes. Available at: https://esa.un.org/unpd/wpp/Download/Standard/Population/. Accessed April 11, 2016.
[d]Note this number represents a downward trend since 2009.
Data sources: UK,[87–89] US,[3,90,91] Australia,[92,93] New Zealand,[92,93] Eurotransplant,[94,95] Scandiatransplant,[96,97] Israel,[98,99] Spain,[98,99] and France.[98–100]

waiting time, reflecting efforts to achieve a more equitable system.[34,35] The "Share 35" scheme was implemented in 2005, which awarded extra priority to pediatric recipients for donors under 35 years and zero HLA-mismatched donors of all ages, but it was unexpectedly associated with a decline in pediatric living donor transplants.[36,37]

Despite repeated efforts to improve the former system, it was perceived as inefficient and inequitable. Over the last decade, the waiting list numbers have doubled, death on the waiting list has increased (Table 1), and average post-transplant survival has deteriorated.[38] By 2011, 39 of 58 DSAs were operating with at least one variance to the national system, resulting in inconsistent allocation across the country.[39] Because waiting time had become the dominant factor of allocation owing to the efforts to improve equity, a system that was essentially a queue was created, with minimal regard for outcomes. As such, kidneys with a long predicted lifespan were often allocated to patients with significantly shorter life expectancy, leading to high rates of death with a functioning graft and unrealized graft benefit. Similarly, younger patients were frequently allocated kidneys with a much shorter life span, resulting in high discard rates, retransplantation rates, and HLA sensitization.[40]

The key concept of the new system is longevity matching, whereby 20% of listed patients with the longest estimated posttransplant survival are prioritized for 20% of the kidneys with the longest estimated graft survival.[28] The estimated posttransplant survival score predicts patient survival on the basis of age, time of dialysis, diabetes status, and prior transplantation. Graft survival is estimated by the kidney donor profile index (KDPI), a continuous measure based on 10 donor characteristics (Table 3). This replaces the previous dichotomous ECD/standard criteria donor stratification of donor kidneys, which inadequately reflected the risk for graft failure.[41] As before, kidneys are allocated through 4 sequences, now defined by the KDPI score of the donor kidney (KDPI $\leq$20%, 20% $>$ KDPI $<$ 35%, 35% $\geq$ KDPI $\leq$ 85%, KDPI $>$ 85%). Pediatric patients retain priority for zero HLA-mismatched kidneys and for kidneys with KDPI $<$35%. Local priority is also retained, but paybacks and local variances are no longer permitted. Changes to the points system include calculating the waiting time from the start of dialysis instead of listing and using a sliding scale of points for the sensitization level.

It is expected that the new scheme will enhance utility by an additional 9000 life years annually and improve transplantation rates for highly sensitized, ethnic minority and patients aged 18 to 49 years. However it is acknowledged that the scheme will likely decrease access to transplantation for patients older than 50 years.[39]

Australia

Previously low donation and transplantation rates in Australia have significantly increased since implementation of the national Organ and Tissue Authority in 2008.[2,42] Remarkably, Australia is now one of few countries where waiting list numbers and median waiting time have decreased over the past decade (Table 1). The decline may be linked to the introduction of national listing criteria that restrict access to the kidney transplant waiting list to patients with an estimated 5-year posttransplant survival of over 80%.[43] These criteria are relatively strict compared with current European

Table 1 | (Continued) Kidney transplant and waiting list figures 2003 versus 2013

Eurotransplant[a]		Scandiatransplant[b]		Israel		Spain		France	
2003	2013	2003	2013	2003	2013	2003	2013	2003	2013
118.8	133.8	24.4	26.1	6.4	7.8	42.5	46.5	60.5	63.8
3991	4586	926	1103	126	264	2051	2552	2127	3074
33.6	34.3	38	42.3	19.7	33.8	48.3	54.9	35.2	48.2
3345	3183	654	756	55	128	1991	2170	1991	2673
28.1	23.8	26.8	29	8.6	16.4	46.8	46.7	32.9	41.9
646	1403	272	347	71	136	60	382	136	401
5.4	10.5	11.1	13.3	11.1	17.4	1.4	8.2	2.2	6.3
12382	11120	1231	1333	469	762	4026	4328	5380	10736
104.2	83.1	50.5	51.1	73.3	97.7	94.7	93.1	88.9	168.3
646	593	20	74	16	30	x	x	113	252
5.4	4.4	0.8	2.8	2.5	3.8	x	x	1.9	3.9
3.3	3.7	1.1	1.2	x	x	x	x	1.4	2.4

guidelines that recommend the exclusion of patients with a life expectancy of less than 2 years.[44]

The national allocation system was introduced in 2011.[43] Only well-matched grafts are allocated nationally (maximum 2 HLA mismatches at HLA-A, -B, or -DR if PRA >80% and at HLA-A or -B only if PRA <80%). Around 20% of kidneys achieve this level of matching, whereas the remaining 80% are allocated locally via state-based algorithms. The national algorithm is based on a points system that starts with a base score from which points are deducted or gained. Priority is given to zero HLA mismatches, sensitized patients at 2 levels (PRA >50% and >80%), pediatric patients (<18 years), waiting time (from start of dialysis), and local patients. Balance of exchange is also considered. Although state-based algorithms differ, all are required to allocate a minimum of 30% of kidneys on waiting time alone to improve equity for difficult-to-match patients.[43]

New Zealand

New Zealand's organ donation and transplantation rates have remained inferior to those of other western countries (Table 1). The donor population in New Zealand is predominantly White, while the ESRD population consists of a high proportion of Maori and Pacific Island nation people. This has led to inequity issues for difficult-to-match patients similar to those observed in the United Kingdom, United States, and Australia.[45]

Access to the waiting list is determined by the same listing criteria used by Australia (estimated 5-year posttransplant survival of >80%), but estimates are calculated using a survival prediction tool based on an index derived and validated in a US dataset of 170,000 patients.[46] Patients are rescored annually or at the time of any change in their health status and are removed from the waiting list if their score falls below 70%.[47]

The structure of the allocation protocol is also similar to the Australian system, whereby patients start with a baseline score from which points are deducted for HLA mismatches and are gained for pediatric status (age <15 years) and waiting time (from start of dialysis).[48] Unlike most other allocation systems, points are not awarded for HLA sensitization because waiting time is considered a good enough surrogate for this. There are 2 levels of allocation: level 1 aims to allocate to well-matched patients (maximum of 2 HLA-A or -B mismatches) and level 2 to long-waiting patients.[49] The structure of the protocol has remained largely unchanged over the past decade, with minor modifications implemented on the basis of audit data. HLA-DR mismatches were excluded from level 1 in 2013 to reduce the percentage of kidneys allocated to this level; age matching was abolished as it became apparent that younger patients were being disadvantaged by the predominantly older donor population; and waiting time was given increased weighting in the points score (personal communication Ian Dittmer). A novel feature of the New Zealand kidney allocation scheme is that all ECD kidneys are biopsied, reviewed by an on-call pathologist, and scored according to the Remuzzi classification. Kidneys scoring 4 to 6 are offered as dual transplants, and those scoring ≥7 are discarded.[49]

Eurotransplant

Eurotransplant was created in 1967 as an international collaboration among Austria, Germany, Belgium, Luxembourg, and the Netherlands and was later joined by Slovenia in 1999, Croatia in 2007, and Hungary in 2013.[50] The vision was to pool together the donor organs and create a centralized waiting list to optimize HLA matching and improve transplant outcomes. However, the early HLA-based kidney allocation system led to a high percentage of highly sensitized, long-waiting, rare HLA phenotype, and HLA-homozygous patients on the waiting list, as well as large imbalances of exchange among the countries.[51]

In 1996, the new Eurotransplant Kidney Allocation System (ETKAS) was introduced to address these issues.[52] This was a points-scoring system based on HLA mismatch, mismatch probability, waiting time, distance between donor and transplant center, national balance of exchange, medical

Table 2 | Transplant characteristics for kidney-only transplants from donors after brain death in the UK 2003 versus 2013

	Actual DBD kidney-only transplants in the UK			
	Jan 1, 2003–Dec 31, 2003		Jan 1, 2013–Dec 31, 2013	
	n	%	n	%
Number of transplants	1133		1161	
HLA mismatches				
Level 1 (000 MM)	193	17.0	216	18.6
Level 2 (0DR+0/1B MM)	588	51.9	437	37.6
Level 3 (0DR+2B or 1DR+0/1B MM)	270	23.8	477	41.1
Level 4 (2B+1DR or 2DR MM)	82	7.2	31	2.7
Matchability				
Easy (1–3)	538	47.5	441	38.0
Moderate (4–7)	429	37.9	512	44.1
Difficult (8–10)	165	14.6	207	17.8
Highly sensitized (cRF >85%)	53	4.7	195	16.8
Waiting time				
<1 yr	497	43.9	236	20.3
1–3 yr	392	34.6	370	31.9
3–5 yr	143	12.6	326	28.1
5–7 yr	48	4.2	159	13.7
≥7 yr	53	4.7	70	6.0
Recipient age				
0–5 yr	10	0.9	7	0.6
6–11 yr	21	1.9	17	1.5
12–17 yr	52	4.6	34	2.9
18–29 yr	122	10.8	107	9.2
30–39 yr	200	17.7	171	14.7
40–49 yr	273	24.1	278	23.9
50–59 yr	266	23.5	269	23.2
60–69 yr	163	14.4	209	18
≥70 yr	26	2.3	69	5.9
Donor-recipient age difference				
<15 yr	688	60.7	732	63.0
15–25 yr	260	22.9	299	25.8
>25 yr	185	16.3	130	11.2
Recipient blood group				
O	467	41.2	512	44.1
A	460	40.6	423	36.4
B	150	13.2	166	14.3
AB	56	4.9	60	5.2
Homozygosity				
HLA-A	161	14.2	148	12.7
HLA-B	90	7.9	84	7.2
HLA-DR	103	9.1	146	12.6
HLA-A,B,DR	16	1.4	29	2.5
Graft number				
1	954	84.2	939	80.9
2	149	13.2	186	16.0
3	24	2.1	31	2.7
4	6	0.5	5	0.4
Diabetic	74	6.5	75	6.5
Gender (male)	697	61.5	717	61.8
Ethnicity				
White	981	86.6	824	71.0
Asian	96	8.5	205	17.7
Black	43	3.8	95	8.2
Other	11	1.0	31	2.7
Not reported	2	0.2	6	0.5
Exchange				
Local center	402	35.5	189	16.3
Local area	399	35.2	604	52.0
Other	332	29.3	368	31.7
Median CIT	18.5 h	(IQR: 15.9–22.4)	14.5 h	(IQR: 11.4–17.9)
1-year graft survival	91.2%	(95% CI: 89.3–92.7)	94.1%	(95% CI: 92.4–95.4)
1-year patient survival	95.5%	(95% CI: 93.9–96.7)	95.9%	(95% CI: 94.2–97.1)

CIT, cold ischemia time; cRF, calculated reaction frequency; DBD, donor after brain death; HLA, human leukocyte antigen; IQR, interquartile range; MM. mismatch.
Data source: NHSBT Data Request. Based on data as of January 20, 2015.[89]

Table 3 | Factors used to calculate the Kidney Donor Risk Index

Donor characteristic
Age
Height
Weight
Ethnicity
History of hypertension
History of diabetes
Cause of death
Serum creatinine
Hepatitis C virus status
Donation after circulatory death status

Source: Organ Procurement and Transplantation Network Policy 8.[28]

urgency, and pediatric age. The Eurotransplant Kidney Allocation System remains in place to date.[50] Points are awarded according to the number of HLA mismatches (0–6), and a unique feature is that equal weighting is given to HLA-A, -B, and -DR loci. Mismatch probability is a measure of the likelihood of finding a 0 or 1 HLA-mismatched donor on the basis of the frequencies of HLA antigens in the Eurotransplant donor pool. Until April 2000, waiting time was counted from the date of registration and thereafter from the date of first dialysis.[51] Pediatric status was previously defined as aged <16 years, but since 2010, those aged >16 years with growth potential proven by an X-ray of the hand are granted pediatric status. Pediatric patients are assigned additional waiting points according to the age of listing, are given double points for zero HLA-mismatched donors, and since 2010, are given priority for donors aged <16 years.[53] Since 2013, previous kidney donors are given a one-off bonus of 500 extra points on registration to the waiting list. A distinctive feature of the Eurotransplant Kidney Allocation System is the inclusion of medical urgency in the allocation score. The Eurotransplant Kidney Allocation System has been successful in transplanting a higher percentage of long-waiting, highly sensitized, rare HLA phenotype, pediatric patients and in equalizing the international imbalances in organ exchange.[54,55]

Eurotransplant was the first organization to develop special allocation programs for specific groups of patients (Figure 2). The acceptable mismatch program was introduced in 1996 for highly sensitized patients (PRA >85%). In the program, it is determined which HLA antigens the patient does not have antibodies against, and priority is given for any donor with acceptable antigens.[56,57] In the Eurotransplant Senior Program started in 1999, non-sensitized recipients aged >65 years are prioritized for donors aged >65 years irrespective of HLA matching. Allocation is based on medical urgency and waiting time only and preferentially on a local basis to minimize cold ischemia time.[58,59] These programs have been successful in increasing the number of transplants and shortening the waiting time for these groups of patients.[60–63]

Scandiatransplant

Scandiatransplant was formed in 1969 as a collaboration among the Nordic countries (Denmark, Finland, Iceland,

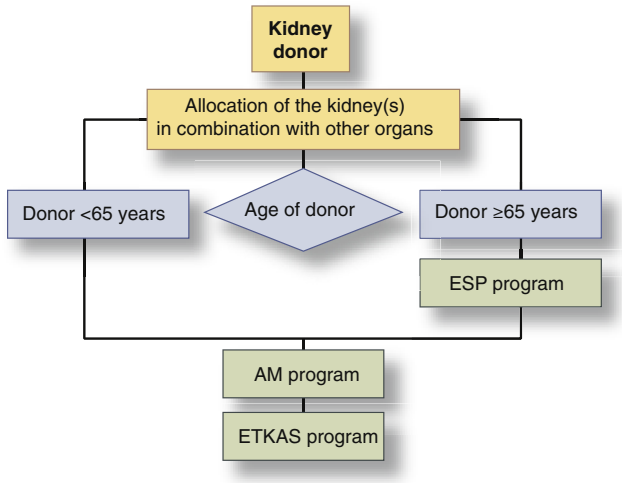

Figure 2 | Eurotransplant kidney allocation flow chart. AM, acceptable mismatch; ESP, Eurotransplant Senior Program; ETKAS, Eurotransplant Kidney Allocation System. Reprinted with permission from Eurotransplant. Eurotransplant Manual Version 5.0. Chapter 4 Kidney (ETKAS and ESP). February 2016. Available at: https://www.eurotransplant.org/cms/index.php?page=et_manual.[50] Accessed April 18, 2016.

Norway, and Sweden). Kidneys were originally exclusively exchanged on the basis of HLA matching, but the current criteria include priority for highly sensitized and pediatric patients.[64] Unlike most schemes, it does not employ the use of a points system. There is a mandatory exchange of at least one donor kidney when a patient on the waiting list has zero HLA mismatches, defined acceptable mismatches as part of the Scandiatransplant acceptable mismatch program (see below), or is a pediatric patient (<16 years at registration) with a maximum of 2 HLA-A or -B mismatches for a donor aged <40 years. Priority is given to highly sensitized patients (PRA ≥80%), followed by those with acceptable mismatches and sensitized patients (PRA 10%–80%). Only blood group-identical exchanges are allowed, and donor-recipient age differences of over 30 years are not permitted. There is a strict control of balance of exchange, and kidneys are required to be paid back within 6 months. For all other kidneys that do not meet the mandatory exchange criteria, allocation is via local transplant center policies.[65]

The Scandiatransplant acceptable mismatch program was introduced in 2009. Patients with PRA ≥80% and a minimum waiting time of 1 year (not necessary for pediatric patients) may be accepted in the program. Within the first 3 years of the program, the number of transplanted highly sensitized patients significantly increased, and the mean waiting time for these patients decreased from 42 to 37 months.[66]

Israel

The Israeli parliament passed the Organ Transplantation Law in 2008 to tackle 3 major barriers to organ donation in Israel.[67] First, it banned the previously legal insurance funding for overseas transplants and declared organ trafficking a criminal offense. Second, it clearly defined brain death in a

way that was acceptable to both the medical and religious communities. Third, it launched a major campaign to promote organ donation on the basis of reciprocal altruism by granting allocation priority to registered organ donors (≥3 years prior to listing), previous living donors, and first-degree relatives of deceased donors. These measures have significantly reduced transplant tourism and increased both living and deceased donation and transplantation rates.[68–70]

The allocation system in Israel is a simple points-scoring system. Points are awarded for waiting time (from the date of first dialysis), age, HLA mismatch, and sensitization level. Age points include priority for pediatric patients and also for younger adults over older ones. There is age matching of donors and recipients aged <18 and >60 years. Points for sensitization are incrementally awarded for each 25% increase in PRA, thereby providing some priority for patients who are moderately sensitized.[71]

Spain

Spain is renowned as a world leader in organ donation.[72,73] Although Spain's "opt-out" system legally allows presumed consent for organ donation, consent from relatives is always sought. The success of the Spanish model is instead attributed for the most part to a network of highly trained donor coordinators.[74] Since the program was introduced in 1989, donation rates have dramatically increased from 14 to 36 donors per million population, which is almost double that of an average European country.[72] Remarkably, donation rates are equal among native and immigrant populations.[2]

The high donation rate in Spain allows for most allocation to occur on a local basis. The criteria vary by region but include waiting time, HLA matching, ABO blood group, age, height, weight, and primary renal diagnosis.[74,75] If a recipient cannot be found on local waiting lists, kidneys are offered regionally and then nationally. There is also a national exchange system for highly sensitized recipients (PRA >80%) and an "old for old" program solely based on age matching.[76]

France

The French national kidney allocation system was first introduced in 1996. Kidneys are allocated on 3 priority levels: local, regional, and national. National priority was given to all zero HLA-mismatched recipients until 2004, and thereafter was restricted to recipients with PRA >5%.[77] Highly sensitized patients (PRA >80%) are prioritized nationally for kidneys with a maximum of 1 HLA mismatch, and since 2004, also for kidneys with "acceptable mismatches".[77] All pediatric recipients are prioritized on a national level for pediatric donors (pediatric definition increased from <16 to <18 years in 2004) and on a regional level for donors aged <30 years.[77] An expert kidney advisory panel can designate national priority for emergency situations such as loss of dialysis access. If a retrieved organ does not trigger any national or regional priorities, it is allocated locally via a points-scoring system introduced in 2006. This includes recipient age, waiting time, HLA mismatch, and donor-recipient age difference.[78]

Discussion

Given the tremendous impact of the kidney allocation policy at both an individual and a societal level, allocation schemes should be continually reviewed and adapted in line with the evolving medical, ethical, and social landscape of kidney transplantation. This review examined the allocation schemes of several countries in which deceased donor kidney transplantation is an accepted and well-established practice. In these jurisdictions, the creation of national transplant organizations has been fundamental to the standardization and regulation of the organ offering process. Local center-based allocation decisions that were largely led by HLA matching and clinician choice have been mostly superseded by national (and sometimes international) protocols that are publicly available, enabling their evaluation. Despite differences in their specific criteria, all of these allocation policies strive for the same core principles of transparency, accountability, and equity of access to kidney transplantation. The importance of this ethical framework for organ allocation is set out in guiding principles by the World Health Organization and in The Declaration of Istanbul.[79,80] Allocation schemes that are designed around the preferences of all relevant stakeholders and are supported by legislation are fundamental to the effective governance of organ donation and transplantation programs. It is evident that in the absence of such oversights, vulnerable populations are at a risk for injustice and exploitation through unethical practices such as organ trafficking, transplant commercialism, and transplant tourism.

A further step forward for improving the objectivity of allocation has been the introduction of points-scoring systems, which can be adjusted according to the changing scientific evidence, clinical practice, or public expectations. Simulation plays an important role in estimating the impact of proposed changes to allocation systems. Specific outcome measures such as life years gained from transplant or the proportion of kidneys allocated to specific patient groups can be simulated with historical data to produce optimal score weights. Although limited by the unpredictable human behavior (i.e., organ acceptance decisions), simulation is becoming a valuable evidence-based tool in allocation system development.

In more ethnically diverse populations, organ sharing based largely on HLA matching has led to a marked inequity of access for ethnic minorities, necessitating more complex algorithms to address this issue. These inequity issues, combined with evidence for a diminishing effect of HLA matching on graft survival in the era of improved immunosuppressive therapy,[81] have prompted revisions to reduce its weighting in most but not all policies. While some countries have eliminated allocation priority for HLA-A and/or -B matching, this has not been widely implemented, and indeed, equal weighting for matching at each of the 3 HLA loci is preserved in some allocation systems (Table 4). Poorly HLA-matched grafts are more likely to result in HLA sensitization, and in the event of graft failure, this jeopardizes the chances

Table 4 | Criteria for deceased donor kidney allocation 2003 versus 2013

	UK		*US*			*Australia*		*New Zealand*	
	2003	**2013**	**2003**	**2013**	**2014**	**2003**	**2013**	**2003**	**2013**
HLA mismatch									
DR	+	+	+	+	+	+	+	+	+
B	+	+	+	-	-	+	+	+	+
A	+	-	-	-	-	+	+	+	+
HLA loci importance	DR > B/A	DR > B	DR > B	DR only	DR only	DR > B/A	DR > B/A	DR > B > A	DR > B > A
Waiting time	+	+	+	+	+	+	+	+	+
Waiting time definition	Listing date	Listing date	Listing date	Listing date	Start of dialysis	Start of dialysis	Start of dialysis	Latest of start of dialysis or listing date	Latest of start of dialysis or listing date
Priority for pediatric recipients	+	+	+	+	+	+	+	+	+
Definition of pediatric recipient	<18 yr	<18 yr	<18 yr	<18 yr	<18 yr	<18 yr	<18 yr, first dialysis <17 yr and on dialysis for >1 yr	<15 yr	<15 yr
Recipient age	+	+[b]	-	-	+	-	-	-	-
Donor-recipient age matching	+	+	-	-	-	-	-	+	-
Priority for highly sensitized recipients	+	+	+	+	+	+	+	-	-
Applicable level of PRA/cPRA (%)	85	85	80	80	20–100[c]	50	50/80[d]	N/A	N/A
Priority for HLA-homozygous recipients	DR	DR, B	-	-	-	-	-	-	-
Local allocation priority	+	+	+	+	+	+	+	-	-
Balance of exchange	+	-	+	+	-	+	+	-	-
Point-scoring systems in use	+	+	+	+	+	+	+	+	+
Special program for allocation of marginal donors	-	-	+	+	+	-	-	-	-
Other allocation criteria/features	Matchability score	Defaulting of rare HLA antigens	Priority for prior organ donors	Priority for prior organ donors	Priority for prior organ donors, EPTS, KDPI	Min 30% locally allocated kidneys on waiting time alone	Min 30% locally allocated kidneys on waiting time alone		EPTS >80% defines eligibility for waiting list, All ECD biopsied and scored by Remuzzi classification

	Eurotransplant		*Scandiatransplant*		*Israel*		*Spain*[a]		*France*	
	2003	**2013**	**2003**	**2013**	**2003**	**2013**	**2003**	**2013**	**2003**	**2013**
HLA mismatch										
DR	+	+	+	+	+	+			+	+
B	+	+	+	+	+	+			+	+
A	+	+	+	+	+	+			+	+
HLA loci importance	DR = B = A	DR = B = A	DR > B/A	DR > B/A	DR > B/A	DR > B/A	?	?	DR = A = B	DR > A/B

(*Continued on next page*)

Table 4 | (Continued) Criteria for deceased donor kidney allocation 2003 versus 2013

	Eurotransplant		*Scandiatransplant*		*Israel*		*Spain*[a]		*France*	
	2003	**2013**	**2003**	**2013**	**2003**	**2013**	**2003**	**2013**	**2003**	**2013**
Waiting time	+	+	-	-	+	+	+	+	+	+
Waiting time definition	Start of dialysis	Start of dialysis	N/A	N/A	Start of dialysis	Start of dialysis	?	?	?	?
Priority for pediatric recipients	+	+	+	+	+	+	+	+	+	+
Definition of pediatric recipient	<16 years	<16 yr or >16 yr and growth potential proven by X-ray of hand	<16 yr at registration	<16 yr at registration	<18 yr	<18 yr	?	?	<16 yr	<18 yr
Recipient age	-	-	-	-	+	+	+	+	-	+
Donor-recipient age matching	-	-	+	+	+	+	+	+	-	+
Priority for highly sensitized recipients	+	+	+	+	+	+	+	+	+	+
Applicable level of PRA/cPRA (%)	85	85	80	80	26–100[c]	26–100[c]	80	80	80	85
Priority for HLA-homozygous recipients	+	+	-	-	-	-	-	-	-	-
Local allocation priority	+	+	-	-	-	-	+	+	-	+
Balance of exchange	+	+	+	+	-	-	-	-	-	-
Point-scoring systems in use	+	+	-	-	+	+	-	-	-	+
Special program for allocation of marginal donors	+	+	-	-	-	-	-	-	-	-
Other allocation criteria/features	Medical urgency, Mismatch probability, AMP, ESP	Medical urgency, Mismatch probability, AMP, ESP, prior kidney donors		STAMP		Priority for registered organ donors of at least 3 yr prior to listing	Height, weight, PRD	Height, weight, PRD, old for old		AMP

AMP, acceptable mismatch program; cPRA, calculated panel reactive antibody; EPTS, estimated posttransplant survival score; ESP, Eurotransplant Senior Program; HLA, human leukocyte antigen; KDPI, Kidney Donor Profile Index; MM, mismatch; PRA, panel reactive antibody; PRD, primary renal diagnosis; STAMP, Scandiatransplant Acceptable Mismatch Program.

[a]No national allocation system. Criteria applicable only at local level.

[b]Age & HLA-MM combined.

[c]Sliding scale of points.

[d]>50% for 000 MM, >80% for all other MM levels.

of HLA-compatible retransplantation. The level of HLA matching, especially HLA-DR matching, is of particular importance in younger patients who are likely to require more than 1 graft over the course of their lifespan. Increased mismatches at first transplant are associated with a higher degree of sensitization, longer waiting time, reduced likelihood of retransplantation, and decreased regraft survival.[82] Many schemes have addressed this by prioritizing younger patients for well-matched grafts. For patients who are highly sensitized, the targeted approach of acceptable mismatch programs, adopted by many countries, has proved successful for improving access to transplantation for these patients. Waiting time has become the dominant factor of allocation in many schemes as concerns over inequity have increased. In the US, this was illustrated by a complete reversal of weighting in allocation; where previously waiting time mostly served as a tie-breaker between 2 similarly HLA-matched recipients, HLA match became the deciding factor between patients with similar waiting times.[83]

The severe shortage of donors, as well as an aging and more infirm population, has led to the increasing use of more "marginal" organs. Despite reduced graft survival, they can offer certain patients improved life expectancy compared with that obtained by staying on dialysis.[32,84,85] However, to optimize any benefit gained, careful donor and recipient selection and matching are required. Remarkably, in some countries, there are no distinct schemes for allocating marginal grafts. While Eurotransplant and Spain have instituted specific "old for old" programs, the UK and France have incorporated donor-recipient age matching into their allocation systems. Nevertheless, these approaches have been criticized for using chronological age as a surrogate of graft function and recipient survival when many other important factors have been described. The previous US ECD scheme was a step forward in classifying the quality of donor organs based on several validated donor risk factors in addition to age. However, the scheme was criticized for the dichotomous stratification of donor kidneys as ECD or non-ECD when in reality, the risk for graft failure is better characterized by a continuous scale.[41] The new US system reflects this with KDPI.[86] This continuous measure of predicted graft survival is used to allocate kidneys on the basis of a recipient's estimated posttransplant survival. Although this applies only to the 20% of recipients with the longest estimated survival, this degree of survival matching is a first in kidney allocation. In New Zealand, a similar prognostic index of posttransplant survival based on multiple patient risk factors is utilized in a novel way to provide an objective criterion (5-year survival >80%) for access to the waiting list. This evidence-based risk stratification ensures those listed have a reasonable expectation of receiving and surviving a transplant. A nationally applicable survival probability threshold for listing is perhaps the most equitable way of determining access to the waiting list, while also ensuring the optimal use of a scarce resource.

The transplant community should be proud of the significant progress that has been achieved in improving the transparency, accountability, and equity of kidney allocation. However, in the context of the continuing shortage of donor organs, further work is required to reduce the discard of donated kidneys and to optimize the efficiency of allocation.

Conclusion

Despite striking shifts in the demographics of donor and recipient populations, there has been relatively little change in deceased donor kidney allocation over the past decade. Given that the donor shortage shows no signs of abatement, it may be timely to consider a radical change in the ideology governing kidney allocation toward "the right kidney to the right recipient." Sophisticated donor-recipient survival matching may well be the optimal compromise between utility and equity that the transplant community strives for.

Search strategy and selection criteria

References for this review were identified by searches of PubMed and Google Scholar using the terms "kidney," "deceased donor kidney," "cadaver kidney," or "kidney transplant" combined with "allocation," "offering scheme," "distribution," or "selection criteria" for publications in any language before April 30, 2016. Data were also obtained by direct contact with national transplant registries, their websites, and reports, including UK Transplant (http://www.odt.nhs.uk/uk-transplant-registry/), US United Network for Organ Sharing (https://www.unos.org/), Australia and New Zealand Dialysis & Transplant Registry (http://www.anzdata.org.au/v1/), Eurotransplant (https://www.eurotransplant.org/cms/), Scandiatransplant (http://www.scandiatransplant.org/), Israel (https://www.adi.gov.il/), Spain Organizacion Nacional de Trasplantes (http://www.ont.es/), and France Agence de la Biomedecine (http://www.agence-biomedecine.fr/).

DISCLOSURE

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All authors contributed to the design of the review. DW conducted the literature review and submitted data requests, DW and GCO drafted the manuscript, and DW, GCO, CW, JAB, JLF, and RJ revised the drafts and approved the final version.

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Access to Transplantation and Transplant Outcome Measures (ATTOM): study protocol of a UK wide, in-depth, prospective cohort analysis

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ABSTRACT

Introduction: There is significant intercentre variability in access to renal transplantation in the UK due to poorly understood factors. The overarching aims of this study are to improve equity of access to kidney and kidney–pancreas transplantation across the UK and to optimise organ allocation to maximise the benefit and cost-effectiveness of transplantation.

Methods and analysis: 6844 patients aged 18–75 years starting dialysis and/or receiving a transplant together with matched patients active on the transplant list from all 72 UK renal units were recruited between November 2011 and March 2013 and will be followed for at least 3 years. The outcomes of interest include patient survival, access to the transplant list, receipt of a transplant, patient-reported outcome measures (PROMs) including quality of life, treatment satisfaction, well-being and health status on different forms of renal replacement therapy. Sociodemographic and clinical data were prospectively collected from case notes and from interviews with patients and local clinical teams. Qualitative process exploration with clinical staff will help identify unit-specific factors that influence access to renal transplantation. A health economic analysis will explore costs and outcomes associated with alternative approaches to organ allocation. The study will deliver: (1) an understanding of patient and unit-specific factors influencing access to renal transplantation in the UK, informing potential changes to practices and policies to optimise outcomes and reduce intercentre variability; (2) a patient-survival probability model to standardise access to the renal transplant list and (3) an understanding of PROMs and health economic impact of kidney and kidney–pancreas transplantation to inform the development of a more sophisticated and fairer organ allocation algorithm.

Ethics and dissemination: The protocol has been independently peer reviewed by National Institute for Health Research (NIHR) and approved by the East of England Research Ethics Committee. The results will be published in peer-reviewed journals and presented at conferences.

Strengths and limitations of this study

- First research programme involving all renal and transplant units in the UK.
- An in-depth analysis (quantitative and qualitative) of access to transplantation and transplant outcome.
- Correlation with patient-reported outcome measures, health status and quality of life.
- Health economic analysis exploring costs and outcomes associated with alternative approaches to organ allocation.
- Limitation due to recruitment process and comorbidity data recorded at enrolment rather than same time point for all study cohorts.

INTRODUCTION

Kidney transplantation is widely regarded to be the best treatment for selected patients with end-stage renal disease (ESRD). When compared with dialysis, transplantation leads to a twofold to threefold increase in life expectancy and, it is often believed, a better quality of life (QoL).[1–4] Over the last decade, transplant survival results have improved progressively and 1-year, 5-year and 10-year graft survival rates are now >90%, >70% and >60%, respectively. For selected patients with ESRD due to type 1 diabetes, combined (or simultaneous) pancreas and kidney (SPK) transplantation offers a better life expectancy compared with renal transplantation alone (70% vs 30% at 10 years[5] and ameliorates diabetes complications).[5 6]

These successes have led to a greater demand for transplantation with an ever

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increasing gap between supply and demand. The demography of patients with ESRD is also changing with an ageing population having more comorbid conditions that may preclude transplantation.[7 8] Currently, fewer than 40% of all patients with ESRD in the UK are listed as suitable candidates for transplantation and only carefully selected patients, without severe cardiovascular disease, undergo an SPK transplant. The need for research on the impact of pretransplant comorbidity on transplant outcome has been identified as a major priority in the UK by the Renal Association.[9]

It is important, in the interest of fairness and equity, that access to the transplant waiting-list is, so far as is possible, standardised, transparent and based on validated criteria. Recent evidence shows that access to transplantation varies between and within the UK centres and differences in assessment for comorbidity are likely to be a major reason.[10] However, even when the effects of comorbidity are accounted for, there remains variation in access to transplantation suggesting that other centre-specific factors are implicated.[11–13] It is unclear which patient-specific and centre-specific factors are responsible for such variations,[11 14] or indeed which centre practices represent the optimal approach. It is also unclear which patient-specific and centre-specific factors impact on outcomes following transplantation but the development of a standardised approach would enable an evidence-based decision-making at individual patient level.

Successful kidney transplantation appears to improve QoL and health status compared with dialysis, but the benefit may not be apparent in all patient groups[15–17] and is not supported by all studies.[18] Furthermore, the impact of kidney–pancreas transplantation on QoL has not been conclusively established.[19] There is a growing body of evidence supporting the cost-effectiveness of transplantation,[20 21] but there are unresolved questions about which patients may benefit the most from transplantation and how organ allocation can be further optimised given scarce supply.

There is considerable interest in the development of organ allocation schemes based on net transplant benefit and significant work has already been undertaken in the context of liver transplantation[22] and cardiothoracic transplantation[23] in the UK and the USA. However, existing kidney allocation policies don't take into account the potential impact of comorbid disease on transplant outcome nor do they address the best use of the increasing number of extended criteria deceased donor organs.[24–28] Recent research has quantified the benefit of kidney and SPK transplantation in order to develop a survival probability model as a basis for listing for transplantation (in the UK)[29] or as a potential allocation model (in the USA).[30] No work has yet been carried out incorporating cost-effectiveness, health status, QoL and other patient-reported outcome measures (PROMs) in any allocation algorithms.

In order to address some of these challenges in transplantation, the UK National Institute for Health Research (NIHR) Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme has been developed by a consortium involving all renal and transplant units in the UK. The overarching aims of the programme are to investigate how we might maximise the net benefit to society from kidney and SPK transplantation, by selecting recipients in a robust and transparent way so as to achieve the best balance between cost, prolongation of life, QoL and acceptability to patients and wider society. The five related research aims of the study are listed below.

1. To identify patient-specific and centre-specific factors that influence (a) access to the transplant waiting-list and to develop a survival probability model as a basis for standardising access to the transplant waiting-list and (b) access to transplantation (deceased donor kidney and pancreas and living donor kidney) for wait-listed patients.
2. To identify patient-specific and centre-specific factors that influence patient survival for transplant wait-listed dialysis patients, after deceased donor kidney transplantation, after SPK transplantation, after living donor kidney transplantation and after pre-emptive transplantation (transplantation as a first mode of renal replacement therapy (RRT) prior to the initiation of dialysis treatment).
3. To evaluate QoL and other PROMs for patients on dialysis, after deceased donor kidney transplantation, after SPK transplantation, after living donor kidney transplantation, after pre-emptive transplantation, in waiting-list controls for kidney and SPK transplantation and in those whose transplants have failed following recruitment to ATTOM.
4. To perform a health economic analysis to explore costs and outcomes associated with alternative approaches to organ allocation.
5. To utilise survival, health status, QoL, treatment satisfaction and costs to determine an optimal organ allocation policy as defined by the maximisation of clinical and cost–benefits derived from transplantation.

We describe the study population and the methodology underpinning the study analyses.

METHODS AND ANALYSIS

Study population

All 72 renal units (of which 23 are renal transplant units) in the UK contributed to the ATTOM programme. Between 1 November 2011 and 31 March 2013, 6360 patients aged 18–75 years were recruited in three cohorts: incident dialysis patients, incident kidney and SPK transplant patients and prevalent listed patients selected as controls for transplanted patients (figure 1). A total of 484 patients moved cohorts (13 patients moved twice) resulting in 6844 registrations within ATTOM (figure 2). In each centre, recruitment took place over a 1-year period aiming to include every

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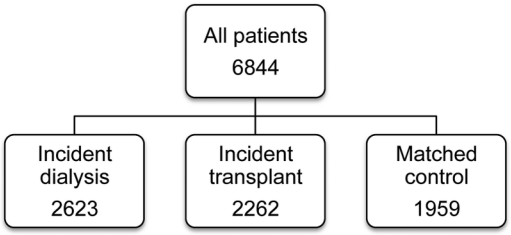

Figure 1 ATTOM, Access to Transplantation and Transplant Outcome Measures (ATTOM) study patient recruitment and cohort distribution.

patient <75 years of age starting RRT. Controls were selected automatically from the UK Transplant Registry database on a fortnightly basis and were matched for: age (within 5 years), time on the list, pre-emptive/on dialysis and the type of transplant (deceased donor or living donor).

Patient-level data (see online supplementary appendix 1) were collected prospectively at the time of starting dialysis, at the time of transplantation or when identified as a control from the transplant list. Dedicated research nurses collected clinical and demographic information from the case notes and local electronic databases, and collected health status and well-being data from patients via completion of the EuroQoL five dimensions (EQ-5D)[31] and 12-item Well-being Questionnaire (W-BQ12).[32–35] The data were uploaded onto a secure website designed, developed and maintained by the UK Renal Registry (UKRR). Data completeness for the items recorded is illustrated in figure 3A, B. Data collection accuracy was ensured using uniform definitions and a training process for the research nurses. An independent data validation of coding of 5% of case notes in all research sites confirmed >98% concordance for all coded fields.

The demographic characteristics of the three study cohorts are illustrated in table 1.

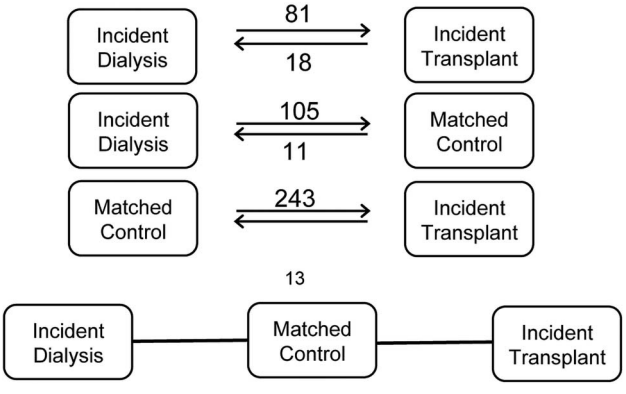

Figure 2 Number of patients changing between the study cohorts and the direction of change.

Analysis

Access to transplantation

Patient-level and centre-level factors influencing access to transplantation for patients starting dialysis are identified through quantitative and qualitative analysis. Patients are followed up for 4 years with data provided by the UKRR/Scottish Renal Registry and the UK Transplant Registry at National Health Service Blood and Transplant (NHSBT) in order to identify whether they are wait-listed for transplant or not, and if wait-listed, whether they received a transplant or not (figure 4). This will inform the analysis of the factors influencing access to listing after starting dialysis and subsequent transplantation.

The qualitative analysis aims to identify systems and processes consistently associated with better (or worse) outcomes in units across the UK, to help define best practice in transplant work-up and listing. This workstream consists of 40 initial qualitative interviews with key stakeholders and patients in a sample of 9 units stratified by proportion of listed dialysis patients, whether transplant or dialysis centre and geography to include spread of deprivation and ethnicity of the catchment area. This is followed by a purpose-designed structured questionnaire for use in a survey of all the UK renal and transplant units. A Delphi consensus study will provide better understanding of professional views on what characterises patients who should (and should not) be assessed for transplant listing and how they should be assessed. The Delphi study, undertaken by emailed electronic questionnaire with two rounds includes transplant surgeons and nephrologists from each centre. Participants are asked to agree or disagree with a series of statements about the eligibility criteria for listing. The initial overall responses are fed back and participants invited to reconsider their views in this second round prior to summarising final levels of agreement. Finally, both patient-level and centre-level factors (from the survey) are explored to determine their influence on transplant listing and subsequent access to transplantation.

Survival with transplantation versus dialysis

Using data derived from the access to transplantation analysis, a multivariate Cox proportional hazards model will estimate the potential risk factors for mortality while on dialysis and their associated HRs, taking into account patient-level and centre-level factors in a multilevel modelling approach. Changes over time in the impact of factors measured at baseline on outcome are modelled using time-varying coefficients. Interactions between variables (eg, age and comorbidity) are included in the final model if significant. This will allow the development of a survival probability prediction tool, which can inform nationally agreed thresholds (such as 'predicted survival >80% at 2 years after start of dialysis') at which a patient should be activated and deactivated on the transplant list. The survival probability tool could be incorporated on a desktop or web-based platform enabling

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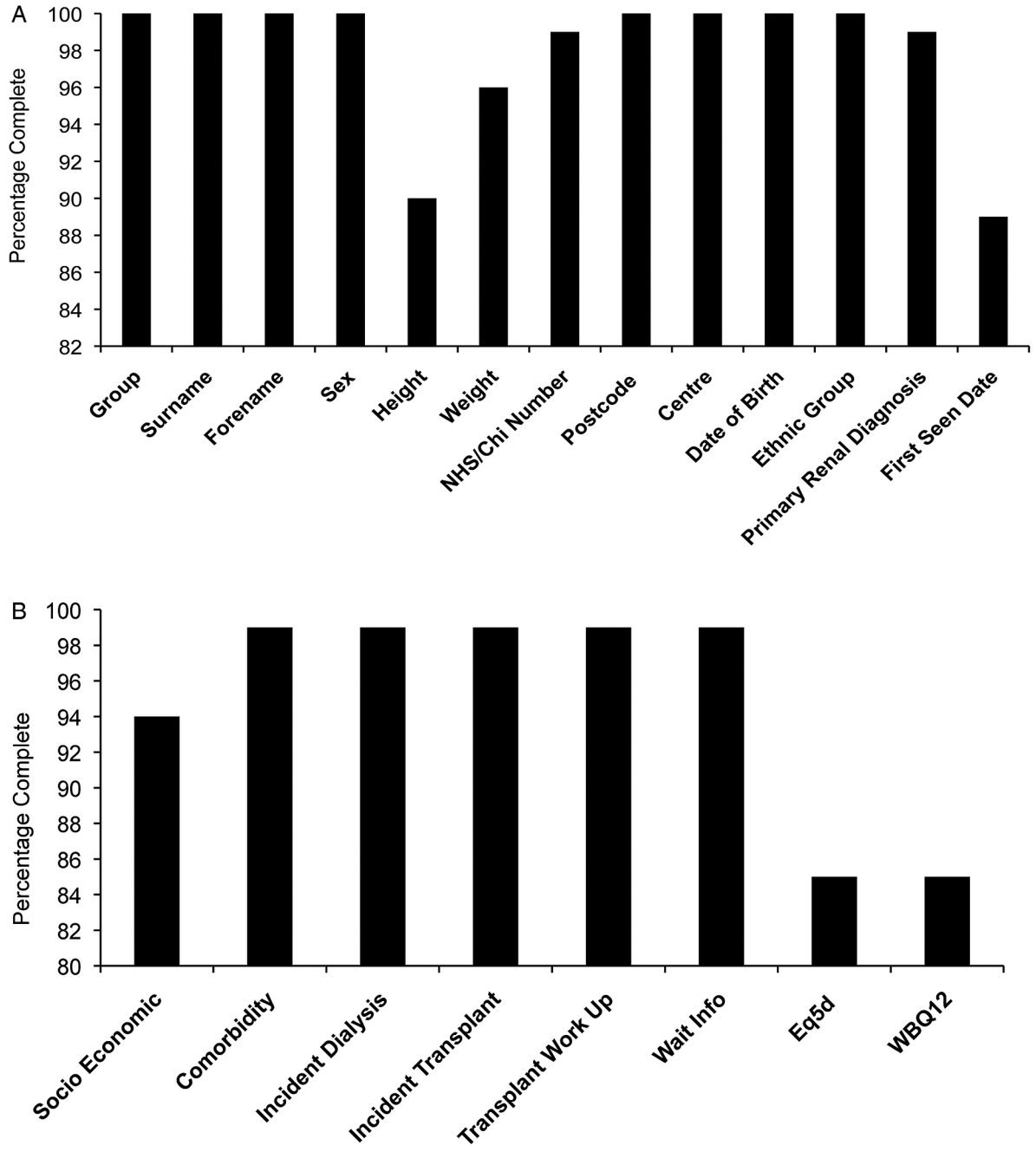

Figure 3 (A and B) Data completeness for each item collected in the study.

clinicians to discuss risk versus benefits with patients when considering transplant listing. A nationally agreed survival probability threshold will also enable robust intercentre comparison to audit listing practices. Follow-up of the dialysis cohort in conjunction with the cohorts illustrated in figure 5, beyond the 5-year duration of this project will enable further refinement of the survival probability assessment tool including the option to predict quality-adjusted life years gained with transplantation.

The study cohorts enable the analysis of patient-specific factors that influence survival for listed patients, after kidney transplantation (live and deceased donors) or after SPK transplantation. A multilevel modelling approach is used to analyse transplantation outcome data and the modelling explores how the outcome variables depend on one or more of the explanatory factors (patient and centre level). The models are developed on the basis of manual variable selection based on clinical and statistical input and are built up by repeatedly incorporating the most statistically significant variable and retesting all others in the presence of included variables, using clinical input to ensure development of a clinically appropriate model. Clinically relevant interactions between variables are predetermined and considered in the model building.

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Table 1 Demographic characteristics of the study cohorts

N	Incident dialysis 2623	Incident transplant 2262	Matched controls 1959
Age at registration to ATTOM			
Mean±SD	56.18±13.55	49.34±13.44	50.38±12.83
Median (IQR)	58.39 (47.48–67.14)	50.28 (40.07–59.89)	51.14 (41.67–60.34)
Gender (%)			
Male	64.93	62.81	57.91
Female	35.07	37.19	42.09
Ethnicity (%)			
White	79.95	82.45	74.54
Asian	11.23	9.40	12.42
Black	7.09	6.21	10.93
Chinese	0.69	0.75	0.92
Mixed	0.65	0.80	0.87
Not specified	0.38	0.40	0.31
Age first seen by nephrologist			
Mean±SD	50.14±15.66	39.85±15.36	39.38±15.41
Median (IQR)	52.76 (39.85–62.68)	40.59 (28.65–51.61)	39.91 (28.24–51.48)

ATTOM, Access to Transplantation and Transplant Outcome Measures.

Evaluation of PROMs

All patients in the ATTOM programme were asked by the research nurses to complete measures of health status (using the EQ-5D and W-BQ12) at or soon after recruitment and at 6 months in those transplanted patients and matched controls on the waiting-list for transplant who were recruited during the first 6 months of nurse data collection. The EQ-5D provides an overall measure of perceived health 'today' and five individual items measuring mobility, pain, self-care, usual activities and anxiety/depression.[31] The W-BQ12 has subscales to measure negative well-being (including depressed and anxious mood), energy and positive well-being over the past few weeks and an overall measure of general well-being.[32–35] In addition, a detailed PROMs study on a subset of 652 ATTOM patients (table 2) recruited in a quasi-random manner (the first eligible patient for each group seen each month by each nurse) is evaluating QoL and the impact of the renal condition on QoL. This uses the individualised Renal-Dependent QoL (RDQoL) measure[36] together with the Audit of Diabetes-Dependent QoL (ADDQoL) for people who also have diabetes[37 38] or a version of the ADDQoL with minor adaptations for people receiving an SPK transplant. These questionnaires are administered at 3 and 12 months post-transplant and at comparable times for those on dialysis. The Renal Treatment Satisfaction Questionnaire status (RTSQs) version[39] is given alongside the RDQoL at each time point, and the Diabetes Treatment Satisfaction Questionnaire status (DTSQs[40 41]) version is given to all those with diabetes (with minor adaptations for those who have received an SPK transplant). In addition, change versions of the RTSQ and DTSQ (the RTSQc and DTSQc)[42–44] are given at 12 months to provide a direct comparison between satisfaction with current treatment and satisfaction with the treatment used before the study began. The EQ-5D and W-BQ12 are also included with the 12-month questionnaires in the detailed PROMs cohorts. The target patient groups and the timing of each questionnaire are summarised in table 3. Transplant recipients completed baseline questionnaires before transplantation where possible (patients receiving pre-emptive transplants) and within a few weeks of

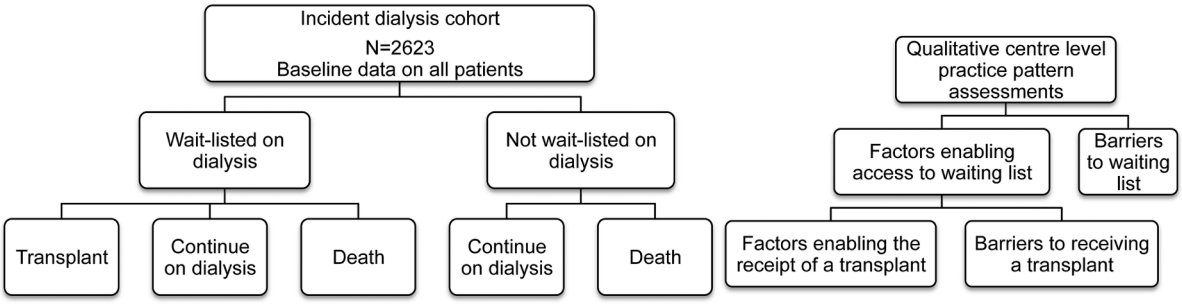

Figure 4 Quantitative and qualitative analysis approach for access to transplantation workstream.

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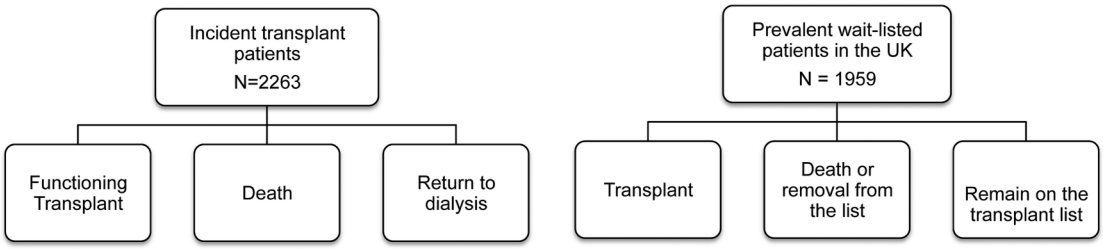

Figure 5 Study cohorts for survival analysis comparison.

transplantation (deceased donor transplants). Patients were given the option to complete the questionnaires via telephone interviews or using mailed paper questionnaires.

Demographic and clinical data are used by the health psychologists alongside QoL and PROMs using multilevel modelling techniques in investigating the factors determining QoL measured by the RDQoL and health status measured by the EQ-5D and exploring the relationship between these two outcomes.

Sixty of the detailed PROMs patients (including patients from each treatment group purposively sampled to include those reporting above and below the mean for their treatment group on RDQoL scores) are included in a qualitative interview study to elicit further information about their experiences, with particular interest in variations in QoL, reasons for satisfaction or dissatisfaction with treatment and their understanding and views about the current and future possible organ allocation schemes.

Health economic analysis

The proposed health economic analysis focuses on the development of a model to simulate different approaches for allocating deceased donor kidneys to patients on the transplant waiting-list. Rather than attempting to identify one optimal allocation scheme, the analysis explores a range of conceptual schemes that reflect varying levels of emphasis on the principles of equity and efficiency. Each allocation scheme is evaluated in terms of cost and health outcomes captured by estimating quality-adjusted life years (QALYs).

Table 2 Detailed PROMs study group

Subgroup	Number of patients
Incident dialysis patients	147
Kidney transplant waiting-list patients	135
SPK transplant waiting-list	29
Deceased donor kidney transplant recipients	120
Living donor kidney transplant recipients	104
SPK transplant recipients	103
Failed transplant	14

PROMs, patient-reported outcome measures; SPK, simultaneous pancreas and kidney.

The model is developed as a discrete event simulation (DES). This approach offers the flexibility to incorporate the influence of patient-level characteristics, such as age and comorbidities, in the estimation of both costs and health gains, to model competing risks and to capture the dynamic consequences of the allocation process for all patients subject to a constrained supply of donor organs.[45] The model is populated using various sources of data with costs of RRT from NHS reference costs and variable hospital costs drawn on patient-level resource use from Hospital Episodes Statistics (HES). Survival for patients on the waiting-list and following transplant is estimated by fitting predictive models to historical data from NHSBT, while health state utility estimates are based on EQ-5D data prospectively collected in the ATTOM study.

Novel allocation schemes

An important outcome of ATTOM is to propose alternative organ allocation policies that consider efficiency and equity factors as well as QoL gains from transplantation utilising data on survival, health status, QoL and financial costs.

Under the current UK allocation scheme, kidneys are allocated according to an algorithm that among other variables favours those who have waited longest and have a better tissue-type match to the donated organ. Apart from avoiding extreme age mismatches, no account is taken of other more complex indicators such as the 'quality' of the kidney, patient QoL and cost-effectiveness of different types of transplant (such as donation after brain death (DBD) or donation after circulatory death (DCD) transplants). Furthermore, no attempt is made to pair estimated graft life with estimated recipient survival. In several countries, there is now great interest in developing organ allocation schemes based on transplant benefit, while the USA has introduced an allocation procedure taking into account the estimated post-transplant survival and the donor kidney quality (as measured by the kidney donor profile index).[30]

The principles of organ allocation procedures based on net benefit involve the calculation of scores that reflect the potential benefit of transplantation based on comprehensive outcome analyses, an individual's life expectancy with and without a given transplant and to prioritise patients who have most to gain. At a point

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Table 3 Tools for QoL and other PROMs analysis, target population and timing of administration

Tool	Time of administration	Patient cohort
EuroQoL five dimensions (EQ-5D) health status tool	Recruitment 6 months 1 year*	All cohorts Those in first 6 months of data collection for transplant and matched control patients Patients in detailed PROMs cohort
Well-Being Questionnaire (W-BQ12)	Recruitment 6 months 1 year*	All cohorts Those in first 6 months of data collection for transplant and matched control patients Patients in detailed PROMs cohort
Renal-Dependent Quality of Life (RDQoL) Questionnaire	3 months* 1 year*	Patients in detailed PROMs cohort
Renal Treatment Satisfaction Questionnaire—status version (RTSQs)	3 months* 1 year*	Patients in detailed PROMs cohort
Renal Treatment Satisfaction Questionnaire—change version (RTSQc)	1 year*	Patients in detailed PROMs cohort
Audit of Diabetes-Dependent Quality of Life (ADDQoL) Questionnaire†	3 months* 1 year*	Patients in detailed PROMs cohort who have diabetes
Diabetes Treatment Satisfaction Questionnaire—status version (DTSQs)†	3 months* 1 year*	Patients in detailed PROMs cohort who have diabetes
Diabetes Treatment Satisfaction Questionnaire—change version (DTSQc)†	1 year*	Patients in detailed PROMs cohort who have diabetes

*Detailed PROMs cohort only.
†Modified versions of these questionnaires were completed by recipients of deceased donor SPK transplants.
PROMs, patient-reported outcome measures; QoL, quality of life; SPK, simultaneous pancreas and kidney.

when a donor organ becomes available, the expected number of days of life without a transplant can be compared with the expected number of days of life following receipt of a transplant. This procedure requires the development of statistical models for survival following wait listing and for survival post-transplantation.

On the basis of the information obtained in the study, we will also explore deceased donor kidney allocation (including kidneys from DCD donors) on the basis of a continuous index of donor organ longevity, along with a continuous index of potential transplant recipients that predicts their likely survival when transplanted over that on dialysis (ie, life years gained due to transplantation). We will incorporate information on QoL into the allocation model by assigning scores for transplantation with different types of organs (ie, DCD or DBD) versus dialysis, informed by the PROMs workstream. Similarly, the cost-effectiveness of transplantation with different types of donor organs could be explored in the model. These data will then be assessed alongside other factors that predict length of wait and survival enabling the development of model (s) which predict an accurate difference in the overall net benefit of a particular type of transplant, thus maximising organ utilisation and the overall benefit for the patients. The impact of potential models of organ allocation will be tested using simulations where the properties of different schemes can be explored and compared, and the impact of policy changes can be forecast. Allocation schemes that focus on different aspects, such as maximum benefit from an organ or equal access to transplantation, can be simulated and the results used to help identify an allocation scheme that provides a balance between efficiency and equity that is acceptable to patients and society.

ETHICS AND DISSEMINATION

Renal transplantation is one of the most successful therapies in modern medicine. However, the landscape of renal transplantation has changed significantly over the last decade with an increasing need, in an older population with more comorbidities and a different donor population, with a higher number of extended criteria donors and DCD. As a consequence, there are a number of major challenges currently facing the provision of renal transplant services. Some of these challenges raise ethical concerns regarding the transparency of the selection process, the consistency of the decision-making process and the equity of access to the transplantation. These issues are at the core of ATTOM and the involvement of patients and ethicists throughout the design and conduct of the study are key to the success of this programme.

Comorbidity, particularly cardiovascular comorbidity, is common in patients with chronic kidney disease (CKD) and may be an important factor leading to inequity in access to transplantation.[10] Previous studies have demonstrated that demographic variables such as gender, age, geographical location and level of social deprivation influence access to transplantation[10 14 46–49] and their interpretation varies significantly between

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centres, raising further concerns about an equal chance of consideration for transplantation. Unlike previous reports, which are retrospective or based on registry analyses, ATTOM is collecting prospective comorbidity data at the time of patients starting dialysis and assesses its impact according to the outcome as shown in figure 4. Furthermore, the planned analyses will enable us to assess further potential inequities in access to transplantation after listing and establish the impact of comorbidity and sociodemographic variables on the outcome of renal transplantation, SPK transplantation and dialysis. The study design and the data collected in ATTOM allow individual patient predictions to be generated, facilitating more informed decision-making. Importantly, it will provide uniformly applicable and explicit evidence-based assessment criteria for entry onto the national transplant waiting-list for kidney and SPK transplantation addressing some of the major ethical concerns highlighted above.

Combining a quantitative and qualitative analysis is one of the novel aspects of ATTOM, allowing an in-depth analysis of individual centre practices, policies and beliefs as well as the views held by patients. By identifying the recipient and organisational factors that most influence access to transplantation and subsequent transplant outcome, the findings will address key ethical concerns and indicate where clinical practice can be changed or refined to achieve fairer and more transparent access to transplantation.

The impact of comorbidity on SPK transplantation outcomes is also unclear, particularly given the more stringent selection criteria for this procedure.[50] There is an ongoing debate regarding the survival benefit of SPK transplantation over and above renal transplantation alone, particularly living donor renal transplantation. ATTOM addresses this issue by directly comparing outcomes in patients taking account of differences in sociodemographics and comorbidity.

There is a strong perception that successful kidney transplantation improves health-related QoL compared with dialysis. One of the ATTOM workstreams addresses these issues providing information on quality of health, QoL, well-being and treatment satisfaction using a combination of established generic instruments as well as recently developed condition-specific measurement tools designed for people with CKD. Furthermore, the study may identify which particular subgroups of patients are likely to gain most or least from transplant because of comorbid disease.

ATTOM includes a health economic analysis that provides insight into long-term cost and survival differences associated with dialysis and transplantation. While the effectiveness of transplantation has already been established, ATTOM considers current clinical pathways and enables further exploration of the impact of donor and recipient factors on both costs and outcomes in the modelling of alternative approaches to allocating organs in the UK.

Organ allocation schemes (addressed in workstream 5) and issues such as which patients should receive priority, which organs should be used and which criteria should inform the allocation decision are at the heart of ethical debates in transplantation.

Data from this study will be curated by the NHSBT and UK Registry providing an ethical reassurance regarding the use of the information collected in the study.

The results of ATTOM will be of direct relevance to patients and their clinicians, and are expected to reshape the provision of renal transplantation in the UK by evaluating the entire CKD pathway from dialysis to transplantation. From a public perspective, ATTOM will provide unprecedented transparency in the decision-making with regard to the use of a scarce national resource. Therefore, we plan to disseminate these findings widely in peer-reviewed journals, at national and international conferences and thorough public engagement days. Furthermore, we intend to engage all relevant stakeholders in the discussions concerning any proposed alternative organ allocation schemes.

In conclusion, ATTOM is the first research programme involving all renal dialysis and renal transplant units in the UK that explores in depth the relationship between access to transplantation and transplant outcomes. The outputs of the study are likely to have a significant impact on the delivery of renal transplantation in the UK.

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Contributors GCO wrote the protocol for workstreams 1 (quantitative analysis), 2 and 5 and coordinated the entire manuscript. RR wrote the protocol for workstreams 1 (quantitative analysis) and 2 and coordinated the entire manuscript. DW contributed to writing the protocol for worsktreams 2 and 5. AG wrote the protocol for worsktream 3. BL wrote the protocol for workstream 4. RP contributed to the protocol in workstream 1. CT contributed to the protocol in workstream 1 (dialysis). JLF contributed to the protocol in worsktreams 1 and 2 (transplant). CB wrote the protocol for workstream 3. JC wrote the protocol for worsktream 4. CD contributed to the protocol in workstream 2 (dialysis) and data collection items definition. CJEW contributed to the protocol in worsktreams 2 and 5 (combined kidney–pancreas transplant and allocation). EMB contributed to coordinating the manuscript. HD provided ethical input in all worsktreams. MR provided statistical input for the protocol in workstreams 1, 2 and 5. LB provided statistical input for the protocol in workstreams 1, 2 and 5. WM contributed

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to the protocol in workstream 1 (dialysis) and data collection items definition. DF contributed to the protocol in workstream 1 (qualitative analysis). PR wrote the protocol for workstream 1 (qualitative analysis and Delphi analysis). JAB contributed to the protocol in worsktreams 1, 2 and 5 and coordinated the manuscript.

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Access to Transplantation and Transplant Outcome Measures (ATTOM): study protocol of a UK wide, in-depth, prospective cohort analysis

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Barriers to living donor kidney transplantation in the United Kingdom: a national observational study

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ORIGINAL ARTICLE

ABSTRACT

Background. Living donor kidney transplantation (LDKT) provides more timely access to transplantation and better clinical outcomes than deceased donor kidney transplantation (DDKT). This study investigated disparities in the utilization of LDKT in the UK.

Methods. A total of 2055 adults undergoing kidney transplantation between November 2011 and March 2013 were prospectively recruited from all 23 UK transplant centres as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) study. Recipient variables independently associated with receipt of LDKT versus DDKT were identified.

Results. Of the 2055 patients, 807 (39.3%) received LDKT and 1248 (60.7%) received DDKT. Multivariable modelling demonstrated a significant reduction in the likelihood of LDKT for older age {odds ratio [OR] 0.11 [95% confidence interval (CI) 0.08–0.17], $P < 0.0001$ for 65–75 years versus 18–34 years}; Asian ethnicity [OR 0.55 (95% CI 0.39–0.77), $P = 0.0006$ versus White]; Black ethnicity [OR 0.64 (95% CI 0.42–0.99), $P = 0.047$ versus White]; divorced, separated or widowed [OR 0.63 (95% CI 0.46–0.88), $P = 0.030$ versus married]; no qualifications [OR 0.55 (95% CI 0.42–0.74), $P < 0.0001$ versus higher education qualifications]; no car ownership [OR 0.51 (95% CI 0.37–0.72), $P = 0.0001$] and no home ownership [OR 0.65 (95% CI 0.85–0.79), $P = 0.002$]. The odds of LDKT varied significantly between countries in the UK.

Conclusions. Among patients undergoing kidney transplantation in the UK, there are significant age, ethnic, socio-economic and geographic disparities in the utilization of LDKT. Further work is needed to explore the potential for targeted interventions to improve equity in living donor transplantation.

Keywords: inequity, kidney transplantation, living donor, pre-emptive transplantation, sociodemographic disparities

INTRODUCTION

For patients with end-stage renal disease (ESRD), living donor kidney transplantation (LDKT) provides better clinical outcomes and more timely access to transplantation than deceased donor kidney transplantation (DDKT) [1–3]. Current UK Renal Association guidelines recommend that LDKT be considered the treatment of choice for all patients suitable for kidney transplantation, whenever an appropriate living donor is available [4]. In contrast to the lengthy waiting time for DDKT, the LDKT procedure can be scheduled without delay, thereby minimizing the time that patients are exposed to pre-transplant dialysis and its associated morbidity, or enabling avoidance of dialysis entirely (pre-emptive

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transplantation). Pre-emptive LDKT is considered by many to be an optimal treatment, providing superior graft and patient survival compared with kidney transplantation following a period of dialysis [2, 4–6].

Despite these advantages, only one-third of kidney transplants undertaken in the UK are from living donors [7]. Internationally, the UK falls behind many other countries in terms of LDKT activity [8]. A recent strategy set out by National Health Service Blood and Transplant (NHSBT) aims to increase LDKT activity in the UK from the current rate of 17 transplants per million population (pmp) to 26 transplants pmp by 2020 [9].

There are limited data on the factors that may prevent or enable patients to receive LDKT in the UK. A better understanding of these factors will facilitate the identification of target patient groups and aid the development of appropriate interventions to improve LDKT rates. The principal aim of this study was to identify the recipient characteristics associated with achieving LDKT compared with DDKT in a national sample of UK kidney transplant recipients. The study was conducted as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme.

MATERIALS AND METHODS

Study population

ATTOM is a national prospective cohort study investigating the factors that influence access, clinical and patient-reported outcomes and cost-effectiveness of renal transplantation in the UK. A full description of the ATTOM study methods and protocol has been reported previously [10]. As part of the ATTOM study, incident kidney transplant recipients were recruited at the time of transplantation from all 23 UK renal transplant centres. In each centre, recruitment took place over a 12-month period, between 1 November 2011 and 31 March 2013. Patients 18–75 years of age were eligible for inclusion. A total of 3002 patients received kidney-only transplants in the UK within the recruitment period; 134 were outside the study age criteria and 775 declined to participate or were not able to be approached for recruitment. In all, 38 of 2093 recruited patients were excluded from the analysis due to missing data for the main outcome variable (living or deceased donor). Thus the final analysis cohort of 2055 patients represented 72% of eligible study participants (Figure 1). There were no significant differences in the age, gender or ethnicity distributions between study participants and the national registry adult kidney transplant recipient population (data not shown) [11].

Data collection

Extensive demographic, socio-economic, clinical and comorbidity data were collected for each patient at the time of transplantation. Trained research nurses collected uniformly defined data items from patient interviews, case notes and local electronic patient information systems.

Ethnicity was coded as White, Black, Asian or other (including patients of Chinese and mixed origin). The level of highest educational attainment was coded as no qualifications, qualifications at the secondary education level or equivalent [e.g. General Certificate of Secondary Education (GCSE), General Certificate of Education Advanced level (A-level), "National Vocational Qualification (NVQ) level 1-3]" or qualifications at

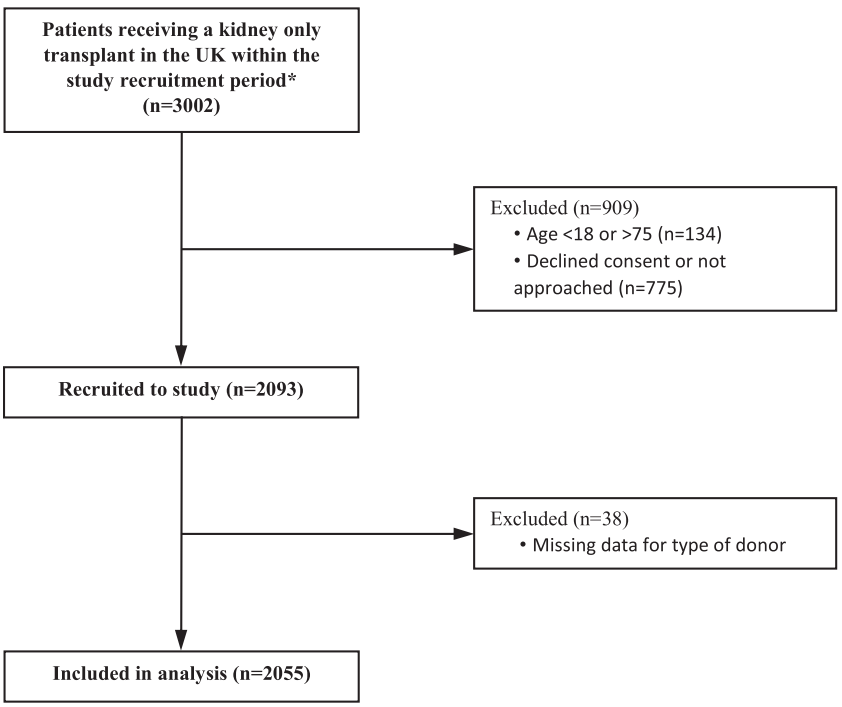

FIGURE 1: Study population (asterisk refers to recruitment that took place over a 12-month period in each centre between 1 November 2011 and 31 March 2013).

the higher education level or equivalent (e.g. bachelor's degree, higher degree, "NVQ level 4–5)". Employment status was coded as employed (including full time, part time or self-employed), unemployed, long-term sick/disabled, retired or other (including those looking after the family home, those not in work for some other reason and students). The primary renal diagnosis was classified by ERA-EDTA codes [12]. Donor details and recipient calculated reaction frequency (cRF) were obtained from linkage to UK Transplant Registry data. The cRF is a measure of recipient human leucocyte antigen (HLA) sensitization, calculated as the percentage of 10 000 recent donors to which the recipient has pre-formed HLA antibodies. A comorbidity score was calculated for each patient using a modified Charlson comorbidity index for patients with ESRD [13]. The index consists of weighted scores assigned to 14 comorbid conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatological disease, peptic ulcer disease, diabetes without complications, diabetes with complications, leukaemia, lymphoma, moderate–severe liver disease and metastatic disease). Our data set did not include two of the conditions (rheumatological disease and peptic ulcer disease). Scores were therefore calculated from the remaining 12 variables.

ORIGINAL ARTICLE

Statistical methods

Baseline characteristics of LDKT and DDKT recipients and donors were compared by chi-squared tests for categorical data and Wilcoxon tests for non-parametric continuous data.

Recipient variables associated with receiving LDKT versus DDKT were analysed using logistic regression. Variables leading to a change in log likelihood at $P < 0.15$ on univariable analysis were entered into the multivariable model. The importance of each variable in the multivariable model was tested by examining the difference in log likelihood between the model with and without the variable. If the difference was not significant ($P > 0.05$) the variable was removed. Each time a variable was removed, the effect of removing each of the remaining variables was retested until the most parsimonious model was achieved. Potential interactions between variables were tested, none were significant. Less than 7% of values were missing for any variable. For modelling purposes, missing values were imputed using the fully conditional specification logistic regression method. In all, 10 imputed data sets were modelled separately then combined to produce final parameter estimates. Sensitivity analysis using casewise deletion of missing values did not change conclusions.

Complex links between socio-economic deprivation and ethnicity with respect to access to and outcomes from renal replacement therapy (RRT) have previously been reported [14, 15]. To avoid any confounding and/or interaction from ethnicity, a subgroup analysis was undertaken in White patients only, using the same multivariable modelling methods as described above.

A second subgroup analysis examined the recipient variables associated with receiving a transplant pre-emptively versus post-initiation of dialysis in the LDKT cohort. Multivariable modelling methods were the same as described above.

All data were analysed using SAS 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Type of transplant received

Of 2055 kidney transplant recipients, 1248 (60.7%) received DDKT (583 donors after brain death and 665 donors after circulatory death) and 807 (39.3%) received LDKT. A significantly higher proportion of LDKT recipients received pre-emptive transplants compared with DDKT recipients (35.5% versus 12.0%; $P < 0.0001$).

Recipient characteristics

There were considerable differences in the characteristics of LDKT versus DDKT recipients (Table 1). LDKT recipients were significantly younger than DDKT recipients (median age 46 versus 53 years) and a higher proportion were of White ethnicity (87.1 versus 79.5%) and married or living with a partner (65.1 versus 60.5%). LDKT recipients were more likely to have obtained qualifications at the secondary education level (53.0 versus 47.9%) and at the higher education level (27.3 versus 18.3%). Compared with DDKT recipients, LDKT recipients had higher rates of employment (43.7 versus 31.3%), car ownership (91.0 versus 80.2%) and home ownership (66.1 versus 62.0%), suggesting they were a less socio-economically deprived population. The cause of renal failure was less likely to be diabetes, hypertension or renal vascular disease in the LDKT group. LDKT recipients had a significantly lower prevalence of comorbidity compared with DDKT recipients. The proportion of kidney transplants that were LDKTs was significantly higher in Northern Ireland (NI) at 68.5%, compared with 39.0% in England, 36.6% in Wales and 31.2% in Scotland.

Donor characteristics

Characteristics of the donors are shown in Tables 2 and 3. Living donors were significantly younger and more likely to be female than deceased donors. A higher proportion of deceased donors were of White ethnicity compared with living donors. A total of 354 (43.9%) living donors were not genetically related to the recipient. Parent, child, other blood relative and spouse living donors were more likely to be female. Pooled/altruistic living donors had the highest proportion of White donors.

Factors associated with the probability of LDKT among transplant recipients

Associations between recipient variables and the likelihood of LDKT versus DDKT were characterized using univariable and multivariable logistic regression (Table 4, Figure 2). The multivariable model demonstrated that with each sequential increase in age group, there was a marked reduction in the probability of LDKT versus DDKT, such that patients 65–75 years of age were ~90% less likely to undergo LDKT compared with patients 18–34 years of age {odds ratio [OR] 0.11 [95% confidence interval (CI) 0.08–0.17], $P < 0.0001$}. Compared with White patients, Asian patients [OR 0.55 (95% CI 0.39–

Table 1. Kidney transplant recipient characteristics by type of donor

	Living donor transplant recipients ($n = 807$)	Deceased donor transplant recipients ($n = 1248$)	P-value*
Demographic variables			
Median age, years	46 (34–56)	53 (44–63)	<0.0001
Age group (years)			<0.0001
18–34	229 (28.4)	128 (10.3)	
35–49	261 (32.3)	359 (28.8)	
50–64	249 (30.9)	526 (42.2)	
65–75	68 (8.4)	235 (18.8)	
Gender			0.191
Male	493 (61.1)	798 (63.9)	
Female	314 (38.9)	450 (36.1)	
Ethnicity[a]			0.0002
White	703 (87.1)	989 (79.5)	
Asian	61 (7.6)	138 (11.1)	
Black	35 (4.3)	94 (7.6)	
Other	8 (1.0)	23 (1.9)	
Socio-economic variables			
Civil status[a]			<0.0001
Married/living with partner	494 (65.1)	697 (60.5)	
Divorced/separated/widowed	66 (8.7)	201 (17.5)	
Single	199 (26.2)	254 (22.1)	
Qualifications[a]			<0.0001
Higher education	207 (27.3)	210 (18.3)	
Secondary education	402 (53.0)	551 (47.9)	
No qualifications	150 (19.8)	390 (33.9)	
Employment status[a]			<0.0001
Employed	332 (43.7)	361 (31.3)	
Unemployed	59 (7.8)	92 (8.0)	
Long-term sick/disability	182 (24.0)	343 (29.7)	
Retired	112 (14.7)	287 (24.9)	
Other	75 (9.9)	71 (6.2)	
Car ownership[a]	691 (91.0)	928 (80.2)	<0.0001
Home ownership[a]	501 (66.1)	716 (62.0)	0.068
Clinical variables			
Primary renal diagnosis[a]			<0.0001
Diabetic nephropathy	48 (6.0)	132 (10.6)	
Glomerulonephritis	229 (28.5)	311 (24.9)	
Polycystic kidney disease	113 (14.1)	209 (16.8)	
Pyelonephritis	127 (15.8)	133 (10.7)	
Hypertensive nephropathy	37 (4.6)	86 (6.9)	
Renal vascular disease	10 (1.2)	27 (2.2)	
Other	156 (19.4)	193 (15.5)	
Uncertain	84 (10.5)	156 (12.5)	
Charlson comorbidity score[a]			<0.0001
0	625 (77.7)	851 (68.4)	
1	91 (11.3)	168 (13.5)	
2	59 (7.3)	136 (10.9)	
≥3	29 (3.6)	90 (7.2)	
Previous transplant	117 (14.5)	157 (12.6)	0.212
Highly sensitized (cRF > 85%)[a]	96 (11.9)	119 (9.5)	0.086
Pre-transplant treatment modality[a]			<0.0001
Haemodialysis	351 (43.7)	718 (57.6)	
Haemodiafiltration	14 (1.7)	39 (3.1)	
Continuous ambulatory peritoneal dialysis	73 (9.1)	204 (16.4)	
Automated peritoneal dialysis	67 (8.3)	130 (10.4)	
Failing transplant	14 (1.7)	6 (0.5)	
Pre-emptive	285 (35.5)	150 (12.0)	
Geographic variables			
Country			<0.0001
England	670 (83.0)	1049 (84.1)	
Wales	34 (4.2)	59 (4.7)	
Northern Ireland	50 (6.2)	23 (1.8)	
Scotland	53 (6.6)	117 (9.4)	

Data are median (IQR) or number (%).

[a]Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Supplementary data, Table S1.

*Wilcoxon test for age. All others chi-squared test.

0.77), P = 0.0006] and Black patients [OR 0.64 (95% CI 0.42–0.99), P = 0.047] were less likely to undergo LDKT than DDKT. Patients who were divorced, separated or widowed had a lower probability of LDKT compared with patients who were married or living with a partner [OR 0.63 (95% CI 0.46–0.88), P = 0.03]. Having no formal qualifications [OR 0.55 (95% CI 0.42–0.74), P < 0.0001] and having only secondary education qualifications [OR 0.76 (95% CI 0.59–0.97), P = 0.01] reduced the odds of LDKT compared with patients with higher education qualifications. Not owning a car [OR 0.51 (95% CI 0.37–0.72), P < 0.0001] and not owning a home [OR 0.65 (95% CI 0.49–0.85), P = 0.002] decreased the odds of LDKT versus DDKT. With adjustment for recipient variables, the odds of LDKT versus DDKT were >3-fold higher for patients in NI [OR 3.25 (95% CI 1.89–5.57), P < 0.0001] compared with patients in England. Further analysis showed the odds of LDKT in NI were also higher compared with Wales [OR 3.77 (95% CI 1.88–7.56), P = 0.0002] and Scotland [OR 4.53 (95% CI 2.42–8.48), P < 0.0001], but there were no significant differences between patients in England, Wales and Scotland.

Table 2. Donor characteristics

	Living donor (*n* = 807)	Deceased donor (*n* = 1248)	P-value*
Median age, years	48 (39–57)	54 (42–64)	<0.0001
Age group[a] (years)			<0.0001
<18	0 (0.0)	28 (2.2)	
18–34	141 (17.5)	156 (12.5)	
35–49	295 (36.6)	296 (23.7)	
50–64	307 (38.1)	497 (39.8)	
65–75	61 (7.6)	236 (18.9)	
>75	2 (0.3)	35 (2.8)	
Gender[a]			0.002
Male	376 (46.7)	671 (53.8)	
Female	429 (53.3)	577 (46.2)	
Ethnicity[a]			<0.0001
White	716 (88.8)	1169 (95.0)	
Asian	50 (6.2)	22 (1.8)	
Black	28 (3.5)	22 (1.8)	
Other	12 (1.5)	17 (1.4)	

Data are median (IQR) or number (%).
[a]Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Supplementary data, Table S1.
*Wilcoxon test for age. All others chi-squared test.

Factors associated with the probability of LDKT among White ethnicity transplant recipients

The same analysis was undertaken in a subgroup of White patients only (*n* = 1692) and confirmed that the effects of socio-economic factors on the likelihood of LDKT versus DDKT were independent of ethnicity (Table 5).

Factors associated with the probability of pre-emptive transplantation among living donor kidney transplant recipients

A further subgroup analysis in the LDKT group examined factors associated with achieving pre-emptive transplantation versus transplantation after the initiation of dialysis (Table 6). Patients with missing data for pre-transplant treatment modality (*n* = 3) and patients with a previous transplant (*n* = 117) were excluded, leaving a final cohort of 687 LDKT recipients. Multivariable analysis demonstrated a significantly decreased likelihood of pre-emptive LDKT for Asian patients [OR 0.45 (95% CI 0.23–0.86), P = 0.016], unemployed patients [OR 0.44 (95% CI 0.21–0.92), P = 0.029], patients unable to work due to long-term sickness/disability [OR 0.44 (95% CI 0.28–0.68), P = 0.0002], retired patients [OR 0.47 (95% CI 0.29–0.75), P = 0.002], not owning a car [OR 0.41 (95% CI 0.19–0.86), P = 0.018] and not owning a home [OR 0.65 (95% CI 0.44–0.96), P = 0.029].

DISCUSSION

Among patients undergoing kidney transplantation in the UK, there are significant age, ethnic, socio-economic and geographic

Table 3. Living donor characteristics by donor–recipient relationship

	Living donors (*n* = 807)						
	Parent [*n* = 147 (18.2%)]	Child [*n* = 75 (9.3%)]	Sibling [*n* = 196 (24.3%)]	Other blood relative [*n* = 35 (4.3%)]	Spouse/partner [*n* = 188 (23.3%)]	Pooled/altruistic [*n* = 93 (11.5%)]	Other non-related [*n* = 73 (9.1%)]
Age group[a] (years)							
18–34	0 (0.0)	51 (68.0)	49 (25.0)	5 (14.7)	10 (5.3)	12 (12.9)	14 (19.2)
35–49	33 (22.5)	24 (32.0)	94 (48.0)	14 (41.2)	69 (36.7)	29 (31.2)	32 (43.8)
50–64	94 (64.0)	0 (0.0)	44 (22.5)	15 (44.1)	94 (50.0)	38 (40.9)	22 (30.1)
65–75	20 (13.6)	0 (0.0)	9 (4.6)	0 (0.0)	15 (8.0)	12 (12.9)	5 (6.9)
>75	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)
Gender[a]							
Male	62 (42.2)	34 (45.3)	99 (50.5)	16 (47.1)	72 (38.3)	50 (53.8)	43 (59.7)
Female	85 (57.8)	41 (54.7)	97 (49.5)	18 (53.0)	116 (61.7)	43 (46.2)	29 (40.3)
Ethnicity[a]							
White	132 (89.8)	64 (85.3)	169 (86.2)	30 (88.2)	170 (90.4)	86 (92.5)	65 (89.0)
Asian	9 (6.1)	5 (6.7)	15 (7.7)	2 (5.9)	11 (5.9)	2 (2.2)	6 (8.2)
Black	2 (1.4)	5 (6.7)	10 (5.1)	2 (5.9)	4 (2.1)	4 (4.3)	1 (1.4)
Other	4 (2.7)	1 (1.3)	2 (1.0)	0 (0.0)	3 (1.6)	1 (1.1)	1 (1.4)

Data are number (%).
[a]Data are missing for some participants and excluded from percentage calculations. Numbers of missing data are shown in Supplementary data, Table S1.

Table 4. Univariable and multivariable logistic regression analysis of factors associated with LDKT versus DDKT

	Univariable		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Demographic variables				
Age group (years)				
18–34	1 (reference)		1 (reference)	
35–49	0.41 (0.31–0.53)	<0.0001	0.34 (0.25–0.46)	<0.0001
50–64	0.27 (0.20–0.34)	<0.0001	0.19 (0.14–0.27)	<0.0001
65–75	0.16 (0.11–0.23)	<0.0001	0.11 (0.08–0.17)	<0.0001
Gender				
Male	1 (reference)			
Female	1.13 (0.94–1.36)	0.192		
Ethnicity				
White	1 (reference)		1 (reference)	
Asian	0.62 (0.45–0.85)	0.003	0.55 (0.39–0.77)	0.0006
Black	0.52 (0.35–0.78)	0.001	0.64 (0.42–0.99)	0.047
Other	0.49 (0.22–1.10)	0.081	0.46 (0.19–1.11)	0.084
Socio-economic variables				
Civil status				
Married/living with partner	1 (reference)		1 (reference)	
Divorced/separated/widowed	0.46 (0.34–0.63)	<0.0001	0.63 (0.46–0.88)	0.030
Single	1.10 (0.88–1.36)	0.406	0.77 (0.58–1.02)	0.067
Qualifications				
Higher education	1 (reference)		1 (reference)	
Secondary education	0.73 (0.58–0.92)	0.009	0.76 (0.59–0.97)	0.010
No qualifications	0.39 (0.30–0.51)	<0.0001	0.55 (0.42–0.74)	<0.0001
Employment status				
Employed	1 (reference)			
Unemployed	0.71 (0.50–1.02)	0.064		
Long-term sick/disability	0.58 (0.46–0.73)	<0.0001		
Retired	0.42 (0.33–0.55)	<0.0001		
Other	1.12 (0.79–1.58)	0.542		
Car ownership				
Yes	1 (reference)		1 (reference)	
No	0.41 (0.31–0.55)	<0.0001	0.51 (0.37–0.72)	0.0001
Home ownership				
Yes	1 (reference)		1 (reference)	
No	0.82 (0.68–1.00)	0.053	0.65 (0.49–0.85)	0.002
Clinical variables				
Primary renal diagnosis				
Diabetic nephropathy	1 (reference)			
Glomerulonephritis	2.03 (1.40–2.94)	0.0002		
Polycystic kidney disease	1.48 (0.99–2.22)	0.054		
Pyelonephritis	2.62 (1.74–3.95)	<0.0001		
Hypertensive nephropathy	1.19 (0.72–1.98)	0.498		
Renal vascular disease	1.02 (0.46–2.26)	0.968		
Other	2.22 (1.50–3.29)	<0.0001		
Uncertain	1.48 (0.97–2.27)	0.068		
Charlson comorbidity score				
0	1 (reference)			
1	0.74 (0.56–0.97)	0.031		
2	0.59 (0.43–0.82)	0.002		
≥3	0.45 (0.30–0.70)	0.0003		
Previous transplant				
No	1 (reference)			
Yes	1.18 (0.91–1.53)	0.212		
Highly sensitized (cRF > 85%)				
No	1 (reference)			
Yes	1.28 (0.97–1.71)	0.087		
Geographic variables				
England	1 (reference)		1 (reference)	
Wales	0.90 (0.59–1.39)	0.642	0.86 (0.54–1.38)	0.539
Northern Ireland	3.40 (2.06–5.63)	<0.0001	3.25 (1.89–5.57)	<0.0001
Scotland	0.71 (0.51–1.00)	0.047	0.72 (0.50–1.03)	0.073

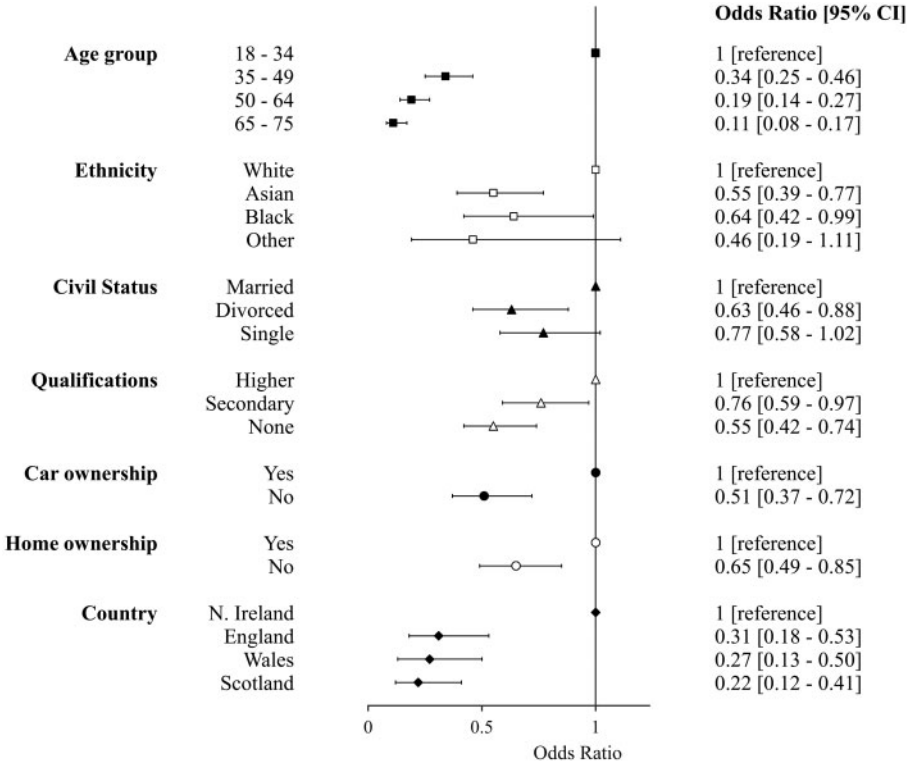

FIGURE 2: Multivariable logistic regression analysis of factors associated with LDKT versus DDKT. N. Ireland, Northern Ireland.

disparities in the utilization of LDKT versus DDKT. Older age; Black and Asian ethnicity; being divorced, separated or widowed; lower educational attainment and measures of greater socio-economic deprivation (non-car and non-home ownership) were significantly and independently associated with a reduced likelihood of LDKT versus DDKT. For the period of the study, geographic differences were also noted, with patients in NI having a greater probability of LDKT versus DDKT compared with patients in the rest of the UK. Furthermore, the study demonstrated that among those who do undergo LDKT, ethnic and socio-economic disparities persist in determining whether LDKT is received pre-emptively. Asian ethnicity, unemployment and greater socio-economic deprivation were associated with a lower likelihood of pre-emptive LDKT versus LDKT after the initiation of dialysis.

A major strength of the present study is that we recruited all patients prospectively and collected accurate, reliable and comprehensive data. A large proportion (72%) of the national adult kidney transplant population was included in the study. Nevertheless, as it was not possible to recruit the entire kidney transplant population, it must be recognized that the study is limited by a risk of selection bias. Reassuringly, the age, gender and ethnicity of study participants were not significantly different from the national adult kidney transplant population [11]. Furthermore, the study cohort included patients from all 23 UK renal transplant centres as well as nationally comparable proportions of LDKT, DDKT and pre-emptive recipients, thereby reducing the potential for bias. However, differences in other unmeasured characteristics between study participants and non-participants cannot be ruled out. Another limitation of the study is that we were unable to account for the fact that some patients may not have had a medically suitable living donor. This could be a potential explanation for the observed lower utilization of LDKT for certain patient groups. It is known that ethnic minorities have a higher prevalence of hypertension and diabetes with associated ESRD, thus precluding kidney donation [16, 17]. Similarly, greater socio-economic deprivation is linked to poorer health [18], potentially limiting the pool of living donors available to more deprived patients. Furthermore, due to the observational nature of the study, the results can only describe associations and thus the causality of the observed relationships cannot be inferred.

In recent years, a great deal of attention has been directed towards disparities in access to DDKT in the UK. Individuals who are older, more socially deprived, from ethnic minority backgrounds or treated in certain transplant centres are less likely to be listed for and subsequently receive DDKT [19–23]. Despite LDKT providing optimal clinical outcomes for patients with ESRD, there have been limited data on whether patients experience disparities in utilizing this treatment. Udayaraj *et al.* [24], reported a lower probability of LDKT for patients with greater socio-economic deprivation and patients from Black and South Asian backgrounds in the UK. However, this study analysed the rates of LDKT among patients starting RRT, therefore a major confounding factor is the poorer health among more socio-economically deprived and ethnic minority populations, leading to a higher proportion of patients being medically unsuitable for transplantation. The present study adds new knowledge about the factors associated with receiving LDKT as opposed to DDKT among a cohort of patients deemed suitable to undergo transplantation. This is a select population of patients who have already successfully navigated the process of

Table 5. Multivariable logistic regression analysis of factors associated with LDKT versus DDKT among White patients only

Recipient variables	OR (95% CI)	P-value
Age group (years)		
18–34	1 (reference)	
35–49	0.31 (0.22–0.44)	<0.0001
50–64	0.17 (0.12–0.25)	<0.0001
65–75	0.11 (0.07–0.17)	<0.0001
Civil status		
Married/living with partner	1 (reference)	
Divorced/separated/widowed	0.60 (0.42–0.86)	0.006
Single	0.70 (0.51–0.96)	0.028
Qualifications		
Higher education	1 (reference)	
Secondary education	0.73 (0.55–0.96)	0.027
No qualifications	0.53 (0.38–0.74)	0.0001
Car ownership		
Yes	1 (reference)	
No	0.50 (0.35–0.73)	0.0003
Home ownership		
Yes	1 (reference)	
No	0.68 (0.50–0.91)	0.01
Country		
England	1 (reference)	
Wales	0.91 (0.56–1.47)	0.693
Northern Ireland	3.43 (1.98–5.95)	<0.0001
Scotland	0.71 (0.49–1.04)	0.076

Table 6. Multivariable logistic regression analysis of factors associated with pre-emptive LDKT

Recipient variables	OR (95% CI)	P-value
Ethnicity		
White	1 (reference)	
Asian	0.45 (0.23–0.86)	0.016
Black	1.19 (0.53–2.65)	0.672
Other	1.17 (0.17–7.79)	0.874
Employment status		
Employed	1 (reference)	
Unemployed	0.44 (0.21–0.92)	0.029
Long-term sick/disability	0.44 (0.28–0.68)	0.0002
Retired	0.47 (0.29–0.75)	0.002
Other	1.41 (0.80–2.50)	0.240
Car ownership		
Yes	1 (reference)	
No	0.41 (0.19–0.86)	0.018
Home ownership		
Yes	1 (reference)	
No	0.65 (0.44–0.96)	0.029

transplant referral, evaluation and listing. Therefore, it is concerning that the striking disparities observed appear to occur over and above the well-recognized inequities that patients face before even reaching this stage. These findings are not confined to the UK. Our results are consistent with those of a USA study by Gore *et al.* [25], which reported lower odds of LDKT relative to DDKT for patients who were older, from ethnic minority groups, with lower socio-economic status and with lower levels of education. Roodnat *et al.* [26], showed the same factors reduced the likelihood of LDKT versus DDKT in The Netherlands. It is interesting that similar results have been demonstrated both within publicly funded as well as private health care systems, suggesting factors other than financial disadvantage play an important role.

The well-recognized markers of socio-economic deprivation (car ownership and home ownership) were strongly associated with a reduced likelihood of LDKT versus DDKT in this study. A subgroup analysis of only White patients confirmed that the effects of socio-economic deprivation were independent of ethnicity. Lower rates of LDKT in socio-economically deprived patients have also been reported in Australia [27] and the USA [28, 29]. The reasons behind this finding are unclear. It is known that living donor–recipient pairs usually come from the same socio-economic group [30]. In the UK, kidney transplantation including medication and aftercare are provided free of charge. However, it is possible that other costs such as transportation, childcare and lost income from time off work could play a role in deterring potential living donors or deterring those in need of a kidney from approaching potential donors [31]. A financial reimbursement policy for expenses incurred by living donors does exist in the UK, but it is not implemented consistently by transplant centres. A recent qualitative study of DDKT recipients found that many were unaware of the living donor reimbursement policy [32]. Despite this, socio-economically deprived patients did not perceive financial concerns to be a major barrier to LDKT and described passivity and disempowerment in treatment decisions, short-term focus and lack of social support as more significant obstacles to LDKT [32].

It is well recognized that ethnic minority patients wait longer for DDKT in the UK, due to the mismatch between the HLA types of minority patients and those of the predominantly White donor pool [33]. One might, therefore, expect a higher uptake of LDKT in ethnic minority patients. Our study found the opposite, with patients from Black and Asian backgrounds having lower odds of LDKT than DDKT compared with White patients. Similar disparities have been reported in the USA [15, 34] and Canada [35]. These disparities have worsened over time and are likely contributing to differences in outcomes between White and non-White patients [36]. The reasons for these disparities are not well understood. Possible explanations cited include cultural and religious beliefs [37, 38], reluctance to engage with the medical system [39, 40], institutional prejudice [41, 42], language barriers [43] and concern over a higher risk for living donors from minority ethnic backgrounds [44–46].

We have demonstrated that a patient's level of educational attainment is independently associated with their likelihood of LDKT versus DDKT. Educational attainment is related to health literacy, which has been shown to be an important factor for both potential kidney transplant recipients as well as potential living donors in successfully navigating the living donation and transplantation process [47, 48]. Higher academic achievement may be linked to a better ability to understand the benefits of LDKT or to take part in informed and shared decision making.

The finding that patients who were married or living with a partner had better access to LDKT is likely to be related to the opportunity for spousal donation. Spouses represented a considerable proportion (23.3%) of living donors in this study, and the

majority were female (61.7%). Being married or living with a partner may also confer other benefits, such as having a better social support network or access to more unrelated or child donors.

Older age was associated with dramatically reduced odds of LDKT versus DDKT. Previous research has demonstrated that older age is associated with a lower probability of attempted donor recruitment [49]. Older patients have reported an unwillingness to put younger donors at risk, particularly their children [50]. In our study, 18.2% of the living donors were parents while only 9.3% were children.

Despite adjustment for demographic and socio-economic factors, we found striking geographic differences in LDKT activity, with patients in NI experiencing higher odds of LDKT versus DDKT compared with patients in England, Wales and Scotland. Our results reflect the actual number of LDKTs pmp, which were around twice as high in NI (31.1) compared with the rest of the UK (England 15.9, Wales 16.6, Scotland 10.9) at the time of the study [51]. Around this time, an initiative was begun in NI to promote LDKT and pre-emptive transplant as the treatment of choice. The key measures included education to promote a change of mindset among nephrologists (particularly non-transplant nephrologists) as well as the entire transplant team, together with improved infrastructure and more streamlined services to enable timely workup and transplantation (e.g. one-stop living donor assessment clinic). Effective leadership, persistence and gaining the support of commissioners and management were critical in achieving these changes [A. Courtney (personal communication, 17 January 2017)]. Our results and the national figures indicate that such a strategy can be very successful in increasing LDKT utilization. The higher LDKT rate in NI led to a lower DDKT rate (NI 15.0, England 24.9, Wales 33.0, Scotland 26.7) [51] and there are now very few long-waiting patients on the waiting list in NI [52]. Moreover, the number of LDKTs in NI has continued to increase (40 pmp in 2016, one of the highest rates in the world), demonstrating that the changes have led to a sustained improvement rather than a temporary peak in activity. This is encouraging when exploring potential avenues to improve LDKT across the UK as a whole.

Our study showed for the first time in the UK that socio-economic deprivation, unemployment and Asian ethnicity were independently associated with a lower likelihood of pre-emptive LDKT. These findings are consistent with studies from the USA and Australia [5, 25, 27]. The disparity experienced by socio-economically deprived individuals is likely to be related to an increased likelihood of late referral to specialist renal services in the UK [53]; however, this does not explain the disparity for patients of Asian ethnicity.

LDKT, and in particular pre-emptive LDKT, provides optimal clinical outcomes for patients with ESRD, yet its uptake is variable within the UK. This study has identified specific patient groups with a lower likelihood of undergoing LDKT relative to DDKT. We have demonstrated that demographic, socio-economic and geographic factors are more strongly associated with the type of transplant received rather than clinical factors, including comorbidity, primary renal diagnosis, HLA sensitization or previous transplantation. Moreover, a remarkable finding is that even among LDKT recipients, disparities persist in receiving pre-emptive transplantation. This demonstrates the strength of social factors in influencing access to health care and may reflect similar inequities across a wide range of health care services. The demonstrated disparities may reflect both barriers in certain patient groups as well as important positive factors in others. Furthermore, these influencing factors are likely to apply to both potential recipients and donors. If particular groups experience avoidable barriers to LDKT receiving or donating, there is a responsibility to provide tailored resources to remove these barriers. Improving access to LDKT will not only benefit individual patients, but will also have favourable effects for the wider ESRD population by effectively increasing the overall pool of available organs. However, both donor and recipient welfare and autonomy undoubtedly remain the primary focus. Some patients may prefer not to pursue LDKT due to concerns about risks to their potential donors, just as some potential donors may be unwilling to donate [50, 54].

Identifying disadvantaged patient groups is essential to directing further research into potentially modifiable factors and appropriate interventions. Several studies in the USA have explored targeted interventions, including culturally sensitive education programmes [55, 56], home-based education [57, 58] and patient advocates [59], with promising results for reducing disparities in LDKT. Similar programmes in the UK may provide a more equitable opportunity for disadvantaged patients to explore the option of LDKT.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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ETHICS APPROVAL

East of England Research Ethics Committee (reference number 11/EE/0120).

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study design. D.W. conducted the literature review and data analysis. M.L.R. and R.J.J. provided statistical input for the data analysis. D.W. and G.C.O. drafted the manuscript. All authors interpreted the data, provided intellectual content, revised the drafts and approved the final version. D.W. and G.C.O. are guarantors for the paper.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract form.

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Patient preferences, knowledge and beliefs about kidney allocation: qualitative findings from the UK-wide ATTOM programme

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ABSTRACT

Objective: To explore how patients who are wait-listed for or who have received a kidney transplant understand the current UK kidney allocation system, and their views on ways to allocate kidneys in the future.

Design: Qualitative study using semistructured interviews and thematic analysis based on a pragmatic approach.

Participants: 10 deceased-donor kidney transplant recipients, 10 live-donor kidney transplant recipients, 12 participants currently wait-listed for a kidney transplant and 4 participants whose kidney transplant failed.

Setting: Semistructured telephone interviews conducted with participants in their own homes across the UK.

Results: Three main themes were identified: uncertainty of knowledge of the allocation scheme; evaluation of the system and participant suggestions for future allocation schemes. Most participants identified human leucocyte anitgen matching as a factor in determining kidney allocation, but were often uncertain of the accuracy of their knowledge. In the absence of information that would allow a full assessment, the majority of participants consider that the current system is effective. A minority of participants were concerned about the perceived lack of transparency of the general decision-making processes within the scheme. Most participants felt that people who are younger and those better matched to the donor kidney should be prioritised for kidney allocation, but in contrast to the current scheme, less priority was considered appropriate for longer waiting patients. Some non-medical themes were also discussed, such as whether parents of dependent children should be prioritised for allocation, and whether patients with substance abuse problems be deprioritised.

Conclusions: Our participants held differing views about the most important factors for kidney allocation, some of which were in contrast to the current scheme. Patient participation in reviewing future allocation policies will provide insight as to what is considered acceptable to patients and inform healthcare staff of the kinds of information patients would find most useful.

Strengths and limitations of this study

- Qualitative methods such as thematic analysis are well suited to understanding the beliefs underlying individual attitudes and opinions of the current kidney allocation system.
- The study interviewed a wide selection of participants, including those currently waiting for a transplant, participants who received a deceased donor or living-donor transplant and those whose transplant failed.
- The interviews were conducted with participants recruited to Access to Transplantation and Transplant Outcomes (ATTOM) so the results cannot be generalised necessarily to all renal patients or other organ allocation schemes.
- Only English-speaking participants were recruited so the results may not reflect fully the views of people of ethnic minority origin. Those patients deemed unsuitable for transplant listing were also not recruited.

INTRODUCTION

Transplantation is widely viewed as the best treatment for most people with advanced chronic kidney disease (CKD).[1] Although transplant rates are increasing, there continues to be a mismatch between supply and demand.[2 3] National kidney allocation policies aim to balance the competing goals of optimising outcomes and providing equity of access to donated organs, in a way that is acceptable to patients and healthcare professionals. In the current UK allocation scheme

for kidneys from deceased heart-beating donors,[4 5] perfectly matched kidneys are prioritised for children (<18 years), patients with antibodies to numerous human leucocyte antigens (HLA) and patients homozygous for HLA-DR. Within these groups, longer waiting patients get priority. Imperfectly matched kidneys are offered to blood-group and HLA-compatible recipients using a points-based system taking into account waiting time and recipient age and HLA-mismatch, aiming to give younger patients better-matched kidneys. Other factors for which points are given include HLA-DR and HLA-B homozygosity, age difference between donor and recipient, blood-group match and geographical location of recipient and donor to minimise extracorporeal kidney storage time. When a donor is identified, kidneys are offered sequentially to wait-listed patients starting with the highest-ranked patient, then the next highest, until accepted. This scheme was introduced in 2006;[4 5] details are available online (http://www.odt.nhs.uk/pdf/kidney_allocation_policy.pdf). Since then, there have been significant changes in donor and recipient demographics, and other factors have emerged as predictors of post-transplant outcomes. In line with the objectives of the scheme,[4] recent discussions suggest a shift in focus towards 'transplant benefit' and matching more carefully the donor and recipient. For this reason, the Kidney Advisory Group of National Health Service Blood and Transplant are reviewing the UK kidney allocation system.

Involving stakeholders in developing kidney allocation schemes helps ensure acceptability.[6] Patients' perspectives and their preferences for factors determining allocation are important for assessing the acceptability of a system and managing patients' expectations of outcomes. Accounting for the outcomes most important to patients may improve patient satisfaction and their ability to make informed decisions regarding listing, but few studies have been conducted on the views of renal patients about kidney allocation schemes. Such studies have indicated broad agreement between factors considered important to patients and those used, such as HLA matching.[7 8] Most UK studies have used discrete choice experiments or questionnaire surveys,[8–10] thus not allowing for further explanation of the reasoning and beliefs behind peoples' preferences or the opportunity to assess how patients interpret questions. Qualitative research, in contrast, provides a deeper understanding of the beliefs underlying individual attitudes and opinions and is capable of identifying unanticipated beliefs or preferences. The objectives of this study were to identify what patients know and think of the current UK kidney allocation system, and what factors they believe should influence allocation.

METHOD

Study context

This qualitative study was conducted as part of the Access to Transplantation and Transplant Outcomes (ATTOM) programme.[11] ATTOM aimed to examine the reasons for disparities in transplant availability[12 13] and learn how to optimise UK transplant outcomes. Research nurses from all 72 UK renal units recruited participants from November 2011 to March 2013. The current study was conducted within a work-stream examining detailed patient-reported outcome measures in 651 patients fluent in English receiving differing treatments for stage 5 CKD, who completed questionnaires on quality of life and treatment satisfaction. Methods have been reported in detail elsewhere.[11] The main aim of the interviews was to explore participant's questionnaire responses related to their quality of life and treatment satisfaction, and additionally explore participants' thoughts about how kidneys are allocated, which is the focus of this paper. Thematic analysis based on a pragmatic approach was used. This is a flexible approach not limited to any one epistemology that acknowledges there are differing ways of making sense of the world. Analyses were conducted in line with established guidelines.[14]

Participants

To ensure inclusion of participants who reported differing levels of negative impact of their renal condition on their quality of life (QoL), participants were selected based on their Renal Dependent Quality of Life (RDQoL) questionnaire[15] scores, completed 12 months following recruitment to ATTOM. The RDQoL is a 21-item disease-specific measure of the impact of CKD on QoL. The impact of CKD on various life domains, and the importance of these domains for QoL, are rated by participants. Impact is multiplied by importance to give a weighted-impact score for each domain. Average weighted-impact (AWI) scores are calculated by dividing the summed weighted-impact scores of each applicable domain by the number of applicable domains, to give a score between −9 (most negative impact) and +3 (most positive impact). Means and SDs were calculated from a subsample of 256 participants. Selecting participants with scores either above or below one SD of the mean allowed for consistent criteria to be used across treatment groups, and selected participants from a wide range of RDQoL AWI scores. Participants were not stratified by demographic variables, but the groups were representative of their cohorts for age, sex and ethnicity, although the living-donor kidney (LD) recipients interviewed were older than the average LD recipient.

Sixty participants were selected to take part (see online supplementary appendix 1); 40 agreed, and 38 were interviewed. Of the 20 who did not participate, 6 declined, 2 were too ill and 12 could not be contacted. Two agreed to participate but could not subsequently be contacted. Two interviews were excluded from analyses (1 wait-listed patient was removed from the list and 1 transplant recipient reported transplant failure at interview).

Interview schedule

An interview schedule was developed (box 1), guided by the published literature.[16] Participants were asked about

Box 1 Questions regarding kidney allocation from the wider interview schedule

The broad questions were asked of all participants. The second set of questions include examples of questions used selectively to obtain further information or explanation from participants.

Broad questions

- Can you please tell me what you know of the current system that is used for allocating kidneys to people on the waiting list?
- Where did you learn about the allocation system?
- If you could decide how the allocation system works, how would you like to see the kidneys being allocated?
- Who do you think should decide who receives a kidney?

Examples of prompts and probing questions

- What factors determine who gets a kidney?
- Can you tell me what you know of how tissue type and blood group influence kidney allocation? Can you tell me how the system tries to reduce the risk of rejection in other ways?
- Can you tell me what you know of how waiting time affects kidney allocation?
- What sort of person do you think is most likely to get a kidney? Why do you think that they have this advantage? Is this fair?
- Do you think that there are other people who should have an advantage? Who? Why?
- What sort of person do you think is least likely to get a kidney? Why do you think so? Is this fair?
- Do you think it is important that everyone has an equal chance of getting a kidney? Why?
- Do you think that sometimes people shouldn't have an equal chance? Who? Why?
- Where did you learn about the allocation system; healthcare staff? Other patients? The internet?
- Was the information you were given consistent with other information you received?
- What factors should be taken into account when deciding who receives a kidney?
- What factors do you think should be given priority? Can you explain why?

their knowledge of the kidney allocation system, and how they would like to see kidneys allocated in future. The interview also included a list of 13 factors that are or could potentially be used to determine allocation (table 1). The list included factors that are used in the UK scheme and those considered important by patients in previous research.[7–10 16] Current determinants of allocation were comprehensibly phrased; for example, cold ischaemia time was referred to as the 'travelling distance between donor kidney and recipient'. Other factors were related to one another, such as likelihood of dying without a transplant and gain in life expectancy, but were assessed separately, in line with previous research.[7] Participants were asked to rate the importance of these factors in deciding priority for who should be allocated a kidney from 0 (not at all important) to 10 (most important). All factors were rated by participants at the end of the interviews, to avoid influencing participants' opinions about the system. Participants were encouraged to elaborate on their answers and to think out loud when making their ratings.

Table 1 Participants' ratings of how important they believe each factor to be in reaching a decision about who receives a kidney transplant as evidenced by mean importance scores

Ranking	Factor	Mean	SD	Range
1	HLA/tissue matching	8.66	1.76	1–10
2	Likelihood of dying without a transplant	8.30	1.72	5–10
3	Age <18 years of potential recipient	8.28	2.09	3–10
4	Blood-group match	8.09	2.33	1–10
5	Gain in quality of health	7.58	2.25	0–10
6	Travelling distance between donor kidney and recipient	7.51	2.76	0–10
7	Age 18–60 years	7.14	2.30	3–10
8	Gain in quality of life	6.73	3.12	0–10
9	Waiting time	6.59	2.31	0–10
10	Gain in life expectancy	6.48	2.97	0–10
11	Number of children of potential recipient	6.24	3.11	0–10
12	Other medical conditions	5.67	2.83	0–10
13	Age 60 years+	5.54	1.90	3–10

Factors rated from 0 (not at all important) to 10 (most important).

Data collection

Semistructured telephone interviews were conducted between December 2013 and August 2014. All participants had been contacted previously by authors (AG or JB) when arranging completion of questionnaires. Postdoctoral research fellow (AG) conducted the interviews. She has qualitative research experience and formal training including the use of NVivo software (QSR International, US) for qualitative analysis. Participants were informed that the interview would explore their questionnaire responses related to their QoL and treatment satisfaction, to broaden the research team's understanding of participant experiences. The interview would also explore participants' thoughts about how kidneys are allocated (box 1). Participants agreeing to take part were phoned at an agreed time for interview.

Data analysis

Interviews were audio-recorded and transcribed. Field notes were made by AG after every interview. Interviews averaged 52 min in length (range =28–91 min). Field notes were reviewed and transcripts read three times for familiarisation prior to analysis. Independent initial coding by AG of 5 interviews established major themes derived from the data which enabled development of a coding framework (AG, CB, MC). This showed significant levels of agreement on independent coding of the

Table 2 Summary of demographic characteristics, time spent on dialysis and on waiting list for the four participant groups

Variable	DD (N=10) M (SD)	LD (N=10) M (SD)	WL (N=12) M (SD)	Tx failed (N=4) M (SD)
Age (years)	52 (14.44)	53 (9.32)	53 (10.65)	53 (12.82)
Time on waiting list (months)	37 (34.48)	– (–)	41 (26.99)	13 (11.59)
Time on dialysis (months)	28 (24.59)	28 (31.67)	39 (31.53)	15 (0.82)
Variable	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex (female)	5 (50%)	5 (50%)	5 (41.6%)	1 (25%)
Diabetes (yes)	3 (30%)	1 (10%)	1 (8.3%)	1 (25%)
Previous transplant failure (yes)	2 (20%)	4 (40%)	6 (50%)	1 (25%)
Treatment modality (pretransplant)				
Predialysis	3 (30%)	3 (30%)	2 (16.7%)	–
Peritoneal dialysis (PD)	1 (10%)	1 (10%)	2 (16.7%)	–
Haemodialysis (HD)	6 (60%)	6 (60%)	8 (66.6%)	4 (100%)
Marital status				
Single	2 (20%)	2 (20%)	3 (25%)	1 (25%)
Living with partner	1 (10%)	–	–	–
Married	5 (50%)	7 (70%)	7 (58.4%)	1 (25%)
Divorced/separated	1 (10%)	1 (10%)	1 (8.3%)	2 (50%)
Widowed	1 (10%)	–	1 (8.3%)	–
Education				
No qualifications	2 (20%)	1 (10%)	–	1 (25%)
Basic (O level/A level/NVQ 1–3)	4 (40%)	6 (60%)	9 (75.0%)	1 (25%)
Higher (degree/higher degree/NVQ 4–5)	4 (40%)	3 (30%)	3 (25.0%)	2 (50%)
Ethnicity				
White	7 (70%)	10 (100%)	8 (66.7%)	4 (100%)
Black	–	–	3 (25%)	–
Chinese	1 (10%)	–		–
Asian	1 (10%)	–	1 (8.3%)	–
Mixed	1 (10%)	–	–	–
Transplant centre				
Belfast	1 (10%)	2 (20%)	–	–
Birmingham	1 (10%)	–	2 (16.7%)	1 (25%)
Bristol	2 (20%)	–	1 (8.3%)	–
Cambridge	1 (10%)	1 (10%)	–	–
Cardiff	1 (10%)	–	1 (8.3%)	1 (25%)
Edinburgh	1 (10%)	4 (40%)	2 (16.7%)	–
Guys	–	–	–	2 (50%)
London West	1 (10%)	1 (10%)	3 (25%)	–
Newcastle	–	–	1 (8.3%)	–
Plymouth	2 (20%)	–	–	–
St. Georges	–	2 (20%)	2 (16.7%)	–

DD, deceased-donor-kidney-transplant group; LD, living-donor-kidney-transplant group; Tx failed, patients whose transplant failed; WL, patients wait-listed for a deceased-donor-kidney-transplant.

next five interviews (AG and JB). There was substantial coder agreement, and AG coded the remaining 26 interviews. The coding was completed in MSWord, then entered into NVivo10 software. Reiteration of earlier responses in later interviews indicated data saturation had been achieved.

RESULTS

Participant characteristics

Table 2 shows participant characteristics. Participants were recruited through 11 UK transplant centres. The sample consisted of 10 deceased-donor (DD) kidney transplant recipients, 10 LD kidney transplant recipients, 4 participants whose transplant failed postrecruitment to ATTOM (Tx failed) and 12 participants wait-listed for a kidney transplant (WL). Four LD recipients received a transplant from a relative (1 parent donor, 3 adult-offspring donors), while 5 received an unrelated transplant through the national paired LD exchange scheme. The donors included in the scheme were relatives (n=1), spouses (n=3) or friends (n=1). One LD recipient received a transplant from a non-directed (altruistic) living donor. Two LD recipients were never wait-listed for a DD transplant. Wait-listed participants were waiting for an average of 41 months. More DD

Table 3 Themes and illustrative quotations

Theme	Subtheme	Illustrative quotations
Certainty of knowledge of the allocation system	Perceived certainty	▶ "Well I know that erm, the individual recipient has to match the donor with a blood type and antibody type and erm, I think there are 6 different numbers you've got to match with, or as near as a match with, before you can actually match up" (Man, WL pre-dialysis). ▶ "It goes by tissue matching. Basically like the lottery. I think you get, there's six things they got to match and the closest match, that's how they allocate the kidneys they give it to the closest match" (Man, DD transplant). ▶ "A lot of it goes on age and um compatibility so I believe the blood group is one of the first things" (Woman, (non-related) LD transplant). ▶ "I understand it's prioritises people who have been on the list for longer, waiting longer" (Man, WL CAPD). ▶ "I know they like to have as good an age match between donors and recipients as possible" (Woman, (non-related) LD transplant). ▶ "As far as I know obviously it's all computerised and it's the best match who gets them" (Woman, (non-related) LD transplant). ▶ "Well as I understand it um at (NHS) Blood and Transplant have a national allocation system. They, that essentially works on a combination of blood type and things like that and tissue typing, the kidneys are allocated on best match but that is flexed by need and time on the waiting list. So you have a combination of best match, overridden by someone who may have an urgent need or someone who spent an extremely long time on the waiting list" (Man, DD transplant).
	Knowledge uncertainty	▶ "I don't know, I don't know what the system is" (Man, HD following failed DD transplant). ▶ 'I don't, I haven't got a clue how they're allocated" (Man, (related) LD transplant). ▶ "I pretty much confess to a certain amount of ignorance because when I had my first one there was a points system and I was a young father, 40, and as I said to you before they wanted to try and transplant a few people early on, so I did, they claim, they say there's not a points system any more but I think probably some people's need is greater than others. And so I'm a little bit in the dark" (Man, WL HD). ▶ "I don't know masses about it I've gotta be honest but my, my guess is they, erm they would look at how match(ed) the kidney is, they would look at how long people have been on the waiting list, they would look at probably age, I would say those are probably the key things, how long you've been on there, what kind of a match it's gonna be for you and what age, say how much kind of benefit you're gonna get from it" (Man, (related) LD transplant). ▶ "Well you get slightly different stories from slightly different people it has to be said. Um you know allegedly there's not a top of the list; right I mean allegedly it kind of works by a points system and all this kind of thing. But, um if you, I mean I only know in my personal circumstance I've been told that you know, I am now near the top of the list so there obviously is a priority sort of system" (Woman, WL predialysis).
Evaluation of the system	Perceived fairness	▶ "I think the guidelines are very fair! I mean it's unfortunate if you've got a, a different metabolism as much as you're a different blood group or your whatever it is, the kidney doesn't match" (Man, DD transplant). ▶ "I think it's fair, you know I don't think anybody should be playing God and deciding ok this person is more needy therefore you get it. Sometimes it's unfair when you see like, somebody who is young, with family and stuff not getting one, but then I wouldn't want to be the person on that board deciding between that person and somebody else. The way they do allocate kidneys is much more neutral" (Woman, DD transplant). ▶ "Not knowing enough about how it's allocated, I would have to assume it's been set up in a good way that it is fairly fair … I would just have to assume that it's been set up in a good way so" (Man, (non-related) LD transplant). ▶ "(It's) probably not a fair system but I mean there's also things like I mean I know it shouldn't matter but I'm not sure geographically um, I mean allegedly it's all one system and you would get a kidney you know from the south of England or whatever but … um technically everybody should have an equal chance, I'm not entirely sure

Continued

Table 3 Continued

Theme	Subtheme	Illustrative quotations
		that's how it works. But I don't think that's necessarily wrong" (Woman, WL predialysis).
	Trust	▶ "Well not knowing enough about how it's allocated, I would have to assume it's been set up in a good way that it is fairly fair but um, so yes I do not know all the ins and outs of the allocation system so I um, I would just have to assume that it's been set up in a good way" (Man, (non-related) LD transplant). ▶ "I suppose the consultant sees the patient and we should all trust the consultants that they're gonna be … if there's fraudulent or back-handed things going on then if we can see everything's kosher and they're making the right decisions for the right reasons" (Woman, predialysis DD transplant). ▶ "I hope that it is (a fair system). I don't have any knowledge of it but I hope that there is and they're not cheating me out of a kidney!" (Man, WL CAPD).
Patient suggestions	Medical priority	▶ "I suppose priority would be um people who really needed it if they were ill. But then I think you have to look at, there's so many points to look at isn't there. You've gotta be healthy enough to receive it. It's no good going through a major operation if you … you've got to be fit enough to have it)" (Woman, HD following failed DD transplant). ▶ "But I think that because of the time and the money it costs I think the money should be best spent and the person most suitable to that kidney … the one that's most likely to be successful" (Man, (related) LD transplant). ▶ "And if it's so much to do with the individual then I guess it has to be um a match, a match basis like they're on cos they, ultimately whether it's going to work or not, medically, whether it's going to work or not, they don't just have to take the gamble medically on that and the best match has to be the thing that takes priority over everything. Always cos then the long-term prognosis is what they care about" (Woman, (non-related) LD transplant). ▶ "If you give a kidney to someone who doesn't best match it, it might only last them an hour or a day and then it's wasted. Someone who's a 100% match it could go forever and forever, you know it could last them forever" (Woman WL HD). ▶ "Well it shouldn't really matter because as I say it's only if it's a proper match. I mean obviously if you've got a guy with a couple of kids and a guy at 60, then it's the same match, a proper match then obviously the younger person should get it. But there's no point. They match the kidneys at present to the age group if they possibly can. I mean there's little point in putting a 60 year old kidney into a 20 year old is there? It's got to be a match" (Man, DD transplant). ▶ "I suppose like people with the worst kidney function obviously need a kidney first" (Man, DD transplant). ▶ "Well it's important to give it to the person who needs it most I think" (Man, DD transplant).
	Increasing life expectancy	▶ "I mean if you had an 85-year-old who's been on the waiting list for goodness knows how long, and you've got a 30-year old and a kidney comes up and it's suitable for both of them, I would have thought that common sense would say the 30-year-old would get it" (Man, pre-dialysis, LD transplant). ▶ "You have to figure out how old are people who receive a kidney, they're more likely to have other health, health side effects than someone who's younger… and also if you're older you know, and you're like a widow or something then your social life is gonna be less than someone who's younger you know, who's just got married and has got kids and stuff like that" (Man, DD transplant). ▶ "I've lived my life. I'm 66 now and if there was a young person lying in bed beside me and two of us could, I would say give it to that, give it to that young life. Yes I would. But that's my personal thought. So I've lived my life, this guy's just starting out, you know" (Woman, DD transplant). ▶ "If you were something like 80 you wouldn't expect to live more than another ten years or something like that, where if you get it when you're 20, you could live another 60 years or something like that. So um, so yes I think it's quite important obviously if it can give a longer, if you're saying if it can give a longer lifespan then it's, um, that should be weighted into it" (Man, (non-related) LD transplant).

Continued

Table 3 Continued

Theme	Subtheme	Illustrative quotations
	Priority based on recipient factors	▶ "Well if that person was the main parent and they got two kids whatever, and if that person doesn't survive because they didn't receive a kidney, and then the kids have to go into care then you know there should be some priority over that [when] you've got two dependants, you know, little ones to look after (rather) than someone who hasn't got anyone (to look after)" (Man, DD transplant). ▶ "I had a two year old child when I first had a transplant so I mean, you could argue that there was a child dependent on me but that, I'm no more special than anyone else" (Woman, WL predialysis). ▶ "That's their fault (they had children)! If you choose to have children, you don't think well if I have more children I'm more likely to get a kidney transplant. No that's not fair" (Woman, pre-dialysis DD transplant). ▶ "I think everyone should be treated equally whatever age" (Woman, DD transplant). ▶ "I may have been more predisposed to say you know that younger ones should have priority, but since my father died I would have argued very strongly that he was entitled to just as many, you know as equal an opportunity as anyone else" (Woman, DD transplant). ▶ "I mean people might say oh yes you know she's a mum and she's got two young children, she should have priority whereas that's chap's 70 and shouldn't … I don't think that's a fair way to do it because who's to say, who's to judge that that person is more deserving of it, or would benefit from it more? I think that has to be a medical decision" (Woman, WL pre-dialysis). ▶ "Why should someone of a younger age be more entitled than someone of an older age?" (Man, (related) LD transplant). ▶ "If a young person has a chance of a decent life but then a middle aged man wants a chance of a decent life, he's got a family. He may be older, he's got a family and you know you can get to my stage of life and still have a family, still have a wife and you still want your shot! I think everybody should have an equal shot" (Man, WL HD).
	Deservingness	▶ "You think about it people go on the transplant list, on the donor list then they should be worth more, get more marks than people who are not on it. So if you've been on the transplant list 20 years, and on the donor list for 20 years and you're an equal match as somebody that's not on the, on the donor list, you should give them priority" (Man, pre-dialysis DD transplant). ▶ "If people are grossly overweight, diabetic you know I mean a lot of, I mean you could argue the case all these people are sort of self-inflicted like you know?" (Man, LD transplant). ▶ "I think people uh, who are extremely ill and who deserve it, which for me would be young people, people with families, that kind of thing" (Man, WL pre-dialysis).

CAPD, continuous ambulatory peritoneal dialysis; DD, deceased-donor-kidney-transplant group; HD, haemodialysis; LD, living-donor-kidney-transplant group; Tx failed, patients whose transplant failed; WL, patients wait-listed for a deceased-donor-kidney-transplant.

recipients reported having fewer educational qualifications, were from a wider range of transplant centres and had greater ethnic diversity than the other groups.

Main qualitative analyses

Three main themes emerged: certainty of knowledge; evaluation of the system and patient suggestions (see online supplementary appendix 2). See table 3 for themes and subthemes.

Certainty of knowledge

Few participants reported detailed knowledge of the system, while many were unsure of how kidneys are allocated. Despite this, the majority correctly identified medical factors such as blood group and HLA typing as important, although all participants referred to HLA matching as 'tissue matching'. Several participants correctly believed that recipient age was a factor, with younger people more likely to be prioritised. One DD recipient felt that there was an upper age limit for receiving a transplant, but was unsure of accuracy: "I think if you're over, I don't know, 60 or 70 you may be less likely to get one… I don't know whether I'm right in that or not, but that's my perception" (Woman, non-related LD transplant).

Some transplant recipients were correctly aware that waiting time is a factor, but very few were aware of how multiple factors combine to determine organ allocation. Some felt more knowledgeable about how factors interrelate than others, but were still uncertain that their information was accurate. Participants whose transplants failed were knowledgeable about HLA typing and its importance in determining allocation. One participant in particular was very knowledgeable of the system,

although he was uncertain about his accuracy: "I believe there's a points system and how that works specifically I don't really know. But I believe that the kidneys would be allocated on what would be the best match, medical match. I believe that children will probably take priority over older people. Whether that's true or not I don't know but that's what I understand. I believe if there is more than; if there's a really good match but more than uh, you know one person that it would be a match to, then that's when I believe the time you've been waiting on the waiting list would then come in. So if there's a donor kidney that would match four people it would go to the person who's been on the list the longest" (Man, on HD following failed DD transplant).

Some participants correctly believed that it is a national allocation system, with a small minority incorrectly believing that wait-listed participants move up the list in a sequential order. Three LD recipients were unsure of the system, but overall, LD recipients and WL participants were more familiar with the points system than the DD recipients who were beneficiaries of this system. WL participants were more likely to report seeking information, and participants whose transplants failed recalled being given information from surgeons and transplant coordinators, while those wait-listed for a transplant and LD recipients mentioned medical staff, seminars and information evenings more often. DD recipients reported receiving written information and researching the scheme on the internet. Most reported being satisfied with the information they received, although a fifth of participants expressed a wish for further information.

Evaluation of the system

When asked to describe the current system, 22 participants made evaluative judgements about its fairness. Patients regarded equity and fairness as synonymous. On the basis of their current knowledge of the system, 17 participants felt that the current system was fair, although 5 felt that it was not. They believed that some people were prioritised over others based on age and/or ethnicity, but did not necessarily believe that the system required change.

Several participants felt that they could trust their doctors, but also felt that if more information was available they could trust them more. One DD recipient believed very strongly that non-related living donation contradicts the information given about matching. Although details of the scheme are available online, this participant felt there was a lack of transparency: "… there's also this sneaking suspicion that someone somewhere gets to make a moral judgement on when the kidneys are handed out and to whom … I'd be much happier if I knew that it was absolutely numerical and somebody wasn't making a judgement call on it at some point … you've got no way of checking that because none of this is in the open" (Man, DD transplant).

Patient suggestions

When participants were asked how kidneys should be allocated, various factors were discussed, including matching, age, perceived medical need, dependants, waiting time and lifestyle factors. These factors were categorised under the themes medical priority, increasing life expectancy, priority based on recipient factors and deservingness.

Medical priority

When asked what factors should be important in deciding who receives a kidney transplant, the main factor recognised spontaneously to be of primary importance by 20 participants was matching (HLA and/or blood), within the context of medical priority. Participants felt so strongly about the importance of matching that many felt non-medical factors such as waiting time were irrelevant: "Your time on the transplant list is governed by if you're a perfect tissue match. That's it. You know you've got, … if it's not a perfect tissue match it's not going to take and if it's not going to take it's not worth having … you've just got to wait. You can't decide well I've waited 5 years I should have the next one" (Man, WL, on HD). Non-medical factors were considered secondary to having a successful, well-matched kidney: "I think what you're looking for is two things, you want the kidney to last and be as close a match as possible" (Woman, DD transplant). Nine participants also felt that people with the most perceived medical need or who are the most ill should be given priority: "Some people may be very, very ill and need the transplant … that should be taken into account" (Man, (related) LD transplant).

Increasing life expectancy

Participants held opposing beliefs about the importance of recipient factors in prioritising kidney allocation. These were often based on beliefs surrounding increasing life expectancy. Many participants felt that young people have yet to live their lives fully, and prioritising them allows them this chance: "I probably think that if you had to choose between a 20-year-old or a 90-year-old, I would probably give it to the younger one because they got their life to live whereas the 90-year-old has lived their life" (Man, DD transplant). At the same time, being older was considered to bring more risk of having other conditions that may complicate the success of a transplant and limit any gains in life expectancy.

Priority based on recipient factors

Although many participants felt that medical priority through matching was important, eight others felt it was unfair for anyone to receive priority based on recipient factors, including time on the waiting list, ethnicity, religion, younger age or having children: "I don't see why one person should have advantage over another" (Woman, (non-related) LD transplant). These participants felt that those who are younger should not receive priority, there should be an equal chance for all to

receive a transplant: "everybody should get an equal chance, just because you're older, you still want to live, you still want to see your grandkids or your great-grandchild" (Woman, WL, on HD). Participants also noted that it would be unfair if those unable or unwilling to have children because of their renal condition were less likely to receive a transplant.

Deservingness

The issue of deservingness was also considered when discussing what factors should be used; two WL participants felt that patients who abuse their body via drugs or alcohol should be given less priority, while one DD transplant recipient believed that those willing to donate organs or who are already on the Organ Donor Register should be given priority if they require a transplant: "People who are willing to donate should be given a bit more priority than people who haven't, as an incentive (to donate)" (Man, DD transplant).

At the end of each interview, participants were asked to rate the importance of 13 factors in deciding priority for who should be allocated a kidney (table 1). Factors relating to medical priority were rated the highest; tissue matching was regarded as the most important, with the likelihood of dying soon without a transplant being considered the second most important factor. Being younger than 18 years of age was considered the third most important. No variable was considered unimportant, although having other medical conditions, being older than 60 years, and having children or dependants were rated as least important for kidney transplant allocation.

DISCUSSION

Although participants in our study were knowledgeable about some aspects of the current UK allocation system, they were not certain their knowledge was accurate. Participants may have been reluctant to place confidence in their knowledge, assuming that the interviewer had greater knowledge than them, though the woman interviewer made no claim to such knowledge. Interestingly, some groups such as those currently wait-listed were more knowledgeable than others. These participants had been wait-listed for 41 months on average and were more likely to report seeking information. In contrast, DD recipients may not have retained information about a system in which they are no longer involved. Although LD recipients received donations outside of the allocation scheme, they were more likely to be aware of the points system than DD recipients. Most were listed for a DD transplant before receiving a LD transplant and fewer LD recipients and WL patients reported having no qualifications. The DD recipients were from a wider range of transplant centres and had greater ethnic diversity. It may be that the differences in knowledge reflect these differences in sociodemographic factors, rather than treatment group, but further work is warranted to assess if this is the case. However, the findings suggest that few participants are confident in their knowledge of the system.

Few participants were aware of the structure of the kidney allocation system, believing that patients receive a kidney in a sequential order. In the absence of full knowledge of the allocation system, participants may attempt to make sense of the system by oversimplifying it through incorrectly anchoring it to their social representation of what constitutes a waiting list.[17] Reference to being on a 'waiting list' may contribute to confusion about the way the system is structured. Perhaps replacing the term 'waiting list' with 'waiting pool' may therefore facilitate more appropriate understanding of how the allocation system works. Although the technical details of the allocation scheme are available online, few participants had accessed this information. Information is more effective if tailored to patients,[18] and there is a risk that highly technical information may not be helpful to most patients. Health literacy is low in patients with kidney disease[19] and patients' knowledge of their disease may be limited,[20] so how best to make information available to patients may need to be reconsidered. In line with previous research from the USA,[21] the majority of participants trusted that the allocation system was fair, while a minority of participants perceived a lack of transparency in how kidneys are allocated. Feeling ill-informed may lead to dissatisfaction with subsequent treatment. Despite this, the majority of participants said they were content with the information they received, so the provision of further medical detail may not be required. Instead, an explanation of how the factors inter-relate in the allocation process may be more useful. Managing expectations of transplantation affects how patients cope post-transplant,[22 23] so it is important that more information be provided about the weight given to matching, and the quality of the kidneys, to help manage patient expectations of transplant survival. Longer waiting times have been shown previously to be an important factor to UK patients,[8 10] but this was not found here. Participants believed that medical priority was the most important; where there is a good match it should be used regardless of waiting time, with a preference for waiting longer for a better-matched kidney. In a US study, Louis *et al*[16] suggested that when patients have seen how detrimental a poor match can be, they may place more value on matching. In the current study, almost half of participants had at least one previous transplant, and all participants whose transplant failed considered matching to be of utmost importance. This may help explain the lack of weight given to waiting time by these participants.

Better matching and younger age were considered the most important factors in determining kidney allocation, which have been identified previously as important to Australian and UK patients.[7 8] Participants were more likely to prioritise children based on the expectation of increasing life expectancy, and being older was

considered to bring more risk of having other conditions that may limit life expectancy, or even preclude transplantation. In contrast, a substantial minority of participants felt that no personal characteristics, including age, should be used to prioritise patients. The reason the current scheme prioritises younger patients for better-matched kidneys is in part to ensure that future transplantation is more easily achieved through avoiding development of antibodies to HLA. The provision of patient-friendly information would explain the reasoning behind prioritising particular groups, which may lead to greater acceptance and understanding of the factors used and of the system overall.

Participants felt that those who have the most medical need for a transplant should be prioritised. There was also acknowledgment that kidneys should be allocated to those who have the best chance of surviving and maintaining a functioning transplant.[7] Allocating kidneys according to medical criteria was considered the best way to allocate organs, which has been found previously in liver transplantation where medical need is assumed to be an objective way to allocate organs, despite the fact that it may require moral judgement.[24] Patients are aware of some of the issues surrounding allocation, but without complete information, patients cannot make well-informed judgements about policies. Previous scheme development has included patient representation, but providing further information to patients about the system may help them feel more confident of their knowledge and opinions as to how the system might be improved.

Although medical need and the use of medical criteria were seen to be important, non-medical and recipient factors were also discussed. For example, having children or dependants was one of the lowest-rated factors, but was raised repeatedly in the interviews. In line with our findings, there is inconsistency in the literature in preferences for this factor, with some UK studies indicating that patients wish to give greater priority to those with dependants,[9] while an Australian study reported more mixed views.[7] Those who do not believe that priority should be based on recipient factors were less likely to consider having dependants as worthy of prioritising patients for kidney allocation, so there is no consensus as to its perceived importance.

A small number of participants felt that patients whose kidneys were damaged by behaviours such as substance misuse were less deserving of a kidney transplant. Other research has shown that participants consider moral deservingness when discussing kidney transplantation.[7] Previous research from the UK and the Netherlands has shown that kidney recipients reported feeling gratitude and a sense of duty to their donors to take care of their kidney,[22 23] so allocating transplants to those considered at risk of not taking care of their kidneys may explain why these factors were considered important in the current study.

The factors rated by participants at the end of the interview showed general agreement with the factors discussed in the interviews. Ratings varied widely, however. Participants found it difficult to distinguish the perceived importance of the factors listed with many showing ceiling effects. In contrast, participants were able to show distinct preferences when asked more general questions about how kidneys should be allocated in the interviews. Although participants were encouraged to elaborate on their ratings, few participants did so, although some of the factors had already been discussed in the interviews. Despite this, the differences in ratings and those factors discussed in interviews suggest that qualitative designs may be more effective in eliciting greater insight into participants' beliefs and preferences.

Strengths and weaknesses of the study

The interviews were conducted with participants recruited to ATTOM, and as with all qualitative studies, the results cannot be generalised to all renal patients or other organ allocation schemes. No attempt was made to achieve a representative sample, so any frequencies given are not necessarily representative of the patient group as a whole. Moreover, comparisons between groups should be noted with caution, as the groups differed in demographic factors such as education level and ethnicity. The interviews were conducted with English-speaking participants from a subsample of transplant centres in the UK. The results therefore may not reflect fully the views of people of ethnic minority origin. Patients deemed unsuitable for transplant listing were not included in the present interview sample. Despite this, collecting qualitative data allowed us to delve further into patients' understanding of the allocation system. This is one of only a handful of studies examining patient beliefs about kidney allocation. Very little research has examined patients' views of kidney allocation and this study is timely to inform forthcoming guideline development and allocation scheme revision. Assessing a large group of patients who have yet to be listed would inform us of what patients know of the system before, during and after listing for a kidney transplant. This study does not provide a comprehensive understanding of patient knowledge, but instead provides a snapshot of such knowledge (or lack of knowledge) may relate to patient suggestions for the allocation scheme.

A representative survey to quantify knowledge, as well as issues regarding age priority, waiting time and the importance of dependants, would help further to describe and understand patient's beliefs and priorities. This study focused exclusively on renal patients; there is a case for considering the views of potential kidney donors and perhaps the wider population for their level of engagement and knowledge of transplantation issues.

CONCLUSIONS

This study highlights that patients vary in their views and their priorities for kidney allocation. Most participants were uncertain of the accuracy of their knowledge. The majority of participants were aware that a number of factors are important, and most were content with their level of knowledge, so tailoring information to allow greater explanation of how factors in the allocation system relate to one another may be important in increasing patients' perceived ability to make informed decisions about the system. Although further work is warranted to assess it, replacing the term 'waiting list' with 'waiting pool' may perhaps facilitate more appropriate understanding of how a points-based allocation system works. Policymakers should continue to consult with patients, as it reveals patient knowledge and understanding, identifies information needs and provides guidelines for what factors may be considered acceptable to patients, which may help increase patients' confidence in being involved in treatment decision-making, and ultimately increase patient satisfaction.

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Contributors AG contributed to the design of the study, developed the interview schedule, conducted the interviews, developed the coding framework, coded and analysed the data, drafted the manuscript and edited and approved the final submission. MC contributed to the design of the study, developed the interview schedule, developed the coding framework, provided feedback on initial drafts of the manuscript and edited and approved the final submission. JB contributed to the design of the study, coded and analysed the data, provided feedback on initial drafts of the manuscript and edited and approved the final submission. DW provided feedback on initial drafts of the manuscript and edited and approved the final submission. HD contributed to the design of the study, developed the interview schedule and edited and approved the final submission. RJJ, CRVT, JLRF, WM, DF, PR, RR and GCO contributed to the design of the study, provided feedback on the interview schedule and edited and approved the final submission. CJEW and JAB conceived the ATTOM programme, contributed to the design of the study, provided feedback on the interview schedule and edited and approved the final submission. CB contributed to the design of the study, developed the interview schedule, developed the coding framework, edited early drafts of the manuscript and edited and approved the final submission.

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Recipient Comorbidity and Survival Outcomes after Kidney Transplantation: a UK-wide Prospective Cohort Study

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Authorship

All authors contributed to the study design. DAW conducted the literature review. DAW and MLR conducted the data analysis. DAW and GCO drafted the manuscript. All authors interpreted the data, revised the drafts and approved the final version.

Disclosure

All authors declared no conflicts of interests.

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Abbreviations

ARD, adjusted risk difference

ATTOM, Access to Transplantation and Transplant Outcome Measures

BMI, body mass index

CI, confidence interval

CIT, cold ischaemia time

CLD, chronic liver disease

cRF, calculated reaction frequency

CVD, cerebrovascular disease

DDKT, deceased-donor kidney transplant

DGF, delayed graft function

ERA-EDTA, European Renal Association – European Dialysis and Transplant Association

ESRD, end-stage renal disease

HF, heart failure

HLA, human leukocyte antigen

HR, hazard ratio

IHD, ischaemic heart disease

LDKT, living-donor kidney transplant

MM, mismatches

PVD, peripheral vascular disease

SE, standard error

UK, United Kingdom

WHO, World Health Organisation

Abstract

Background: Comorbidity is increasingly common in kidney transplant recipients, yet the implications for transplant outcomes are not fully understood. We analysed the relationship between recipient comorbidity and survival outcomes in a UK-wide prospective cohort study – ATTOM.

Methods: 2100 adult kidney transplant recipients were recruited from all 23 UK transplant centres between 2011-2013. Data on 15 comorbidities were collected at the time of transplantation. Multivariable Cox regression models were used to analyse the relationship between comorbidity and 2-year graft survival, patient survival and transplant survival (earliest of graft failure or patient death) for deceased-donor kidney transplant (DDKT) recipients (n=1288) and living-donor kidney transplant (LDKT) recipients (n=812).

Results: For DDKT recipients, peripheral vascular disease (HR 3.04, 95%CI 1.37, 6.74, p=0.006) and obesity (HR 2.27, 95%CI 1.27, 4.06, p=0.006) were independent risk factors for graft loss, while heart failure (HR 3.77, 95%CI 1.79, 7.95, p=0.0005), cerebrovascular disease (HR 3.45, 95%CI 1.72, 6.92, p=0.0005) and chronic liver disease (HR 4.36, 95%CI 1.29, 14.71, p=0.018) were associated with an increased risk of mortality. For LDKT recipients, heart failure (HR 3.83, 95%CI 1.15, 12.81, p=0.029) and diabetes (HR 2.23, 95%CI 1.03, 4.81, p=0.042) were associated with poorer transplant survival.

Conclusion: The key comorbidities that predict poorer 2-year survival outcomes after kidney transplantation have been identified in this large prospective cohort study. The findings will facilitate assessment of individual patient risks and evidence-based decision making.

Keywords: kidney transplantation, outcomes, survival prediction, comorbidity

Introduction

Kidney transplantation is widely regarded as the treatment of choice for end-stage renal disease (ESRD). However, outcomes after transplantation vary considerably between patients and prediction of individual risk is challenging due to the increasing prevalence of complex comorbidity among the ESRD population. Conditions such as diabetes, hypertension and obesity which contribute to the development of ESRD are on the rise,[1] while ESRD itself is an important risk factor for other comorbidities such as cardiovascular disease.[2, 3] Over the past decade, the proportion of deceased-donor kidney transplant (DDKT) recipients older than 60 years of age has increased from 17% to 29% in the UK,[4] and the burden of comorbidity among patients undergoing kidney transplantation has also risen significantly.[5-7]

Despite this, there are limited data on the impact of comorbidity on transplant outcomes. A small number of studies have demonstrated the overall detrimental effect of comorbidity on transplant outcomes using various comorbidity indices.[5, 8-10] However, this does not allow characterisation of the risks associated with specific comorbid conditions.. Retrospective registry analyses have identified several comorbidities as risk factors for transplant outcomes, but the results show considerable heterogeneity and are limited by the reliability of the data.[11-13] Up-to-date and reliable evidence is essential to enable clinicians to fully inform patients of their individual risks and likely outcomes, thereby facilitating shared decision-making and informed consent.

We conducted a national prospective cohort study to investigate the impact of a wide range of baseline comorbid conditions on survival outcomes following kidney transplantation. We report the two-year survival outcomes of the study which was conducted as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme.

Materials and Methods

Study design and participants

ATTOM is a national prospective cohort study investigating the factors that influence access to and outcomes from renal transplantation in the UK. A full description of the ATTOM protocol has been reported previously.[14] A cohort of 2262 incident kidney transplant recipients were recruited to ATTOM at the time of transplantation, from all 23 UK renal transplant centres. In each centre recruitment took place over a 12-month period between 1st November 2011 and 31st March 2013. Patients aged 18-75 years were eligible for recruitment. For the purposes of this analysis, multi-organ transplant recipients (n=162) were excluded. The final study sample (n=2100) represented 73% of eligible study participants from the national kidney-only transplant population (Figure 1). Patients were followed up for two years from the date of transplant. DDKT recipients (n=1288) and living-donor kidney transplant (LDKT) recipients (n=812) were analysed separately.

Data variables

The variables of interest were recipient comorbidities at the time of transplantation comprising diabetes, ischaemic heart disease (IHD), heart failure (HF), atrial fibrillation, cardiac valve replacement, pacemaker, cerebrovascular disease (CVD), peripheral vascular disease (PVD), abdominal aortic aneurysm, chronic respiratory disease, chronic liver disease (CLD), blood borne viruses, malignancy, mental illness (definitions given in Supplementary Table S1) and body mass index (BMI).

The primary outcome measures were graft survival, patient survival and transplant survival. Graft survival was defined as the time from transplantation to graft failure (earliest of return

to dialysis or re-transplantation), with censoring for death with a functioning graft, at last follow-up or at two years. Patient survival was defined as the time from transplantation to patient death, with censoring at last follow-up or at two years. Transplant survival is a composite outcome defined as the time from transplantation to the earliest of graft failure or patient death, with censoring at last follow-up or at two years.

Potential confounders considered in multivariable analyses included (a) recipient variables: age, gender, ethnicity, primary renal disease (as classified by ERA-EDTA codes[15]), time on dialysis, previous transplantation, sensitisation level, smoking status; (b) donor variables: age, gender, ethnicity, BMI; (c) transplant variables: human leukocyte antigen (HLA) mismatches (MM), cold ischaemia time (CIT), delayed graft function (DGF). Ethnicity was coded as White, Black, Asian and Other (including Chinese and mixed origin). Recipient calculated reaction frequency (cRF) ≥85% was used to define highly sensitised recipients. The cRF is the percentage of a pool of 10,000 UK donors to whom the recipient has unacceptable HLA antibodies. HLA mismatches were classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme: level 1 (000 HLA-A, B, DR MM), level 2 (0DR + 0/1B MM), level 3 (0DR + 2B MM) or (1DR + 0/1B MM) and level 4 (1DR + 2B MM) or (2DR MM).[16]

Data collection

Baseline recipient variables (including comorbidity) were collected by trained research nurses at the time of transplantation from patient interviews, case notes, local electronic patient information systems and/or confirmed with the patient's named consultant nephrologist. Independent validation of 5% of data entries in all research sites confirmed >98%

concordance for all data fields.[14] Donor and transplant variables and 2-year graft and patient survival data were obtained through linkage with the UK Transplant Registry.

Statistical methods

Baseline characteristics were compared with chi-squared tests for categorical data and Mann–Whitney U tests for non-parametric continuous data. The impact of comorbidity on two-year survival outcomes was examined using Kaplan-Meier estimates and Cox proportional hazards regression models. DDKT and LDKT recipients were analysed separately. As there were no significant differences in outcomes between recipients of donors after circulatory death and donors after brain death, all DDKT recipients were analysed together. For DDKT recipients, separate multivariable models were built for the three different outcomes of transplant, graft and patient survival. For LDKT recipients, modelling was only possible for transplant survival, as the lower number of graft failures and patient deaths prevented modelling of graft and patient survival separately. All comorbidities were considered for inclusion in the multivariable models, and those leading to a significant ($p<0.05$) change in log likelihood were retained using a manual backward elimination method. Models were adjusted for statistically significant variables as well as variables selected *a priori* on the basis of clinical relevance. Continuous variables were explored as linear, fractional polynomials and categorical variables. In all models, the effect of the time on dialysis variable was only found to be significant after 3 years, and thus it was converted to a binary variable (<3 years versus ≥ 3 years) as this provided the best fit in each model. The relationship between recipient BMI and graft survival was also found to be better represented by converting BMI to a categorical variable, in accordance with the World Health Organisation (WHO) BMI classifications.[17] Potential interactions between all variables were tested, none were significant. The proportional hazards assumption was found to be satisfied for all variables after checking log

cumulative hazards plots and Schoenfeld residuals. Frailty models were used to check for inter-centre variation by using the likelihood ratio test to assess the change in -2LogL after inclusion of transplant centre as a random effect. The adjusted risk difference (ARD) was calculated using methods described by Laubender et al.[18] The ARD describes the absolute effect of the comorbidity risk factor on survival probabilities after adjustment for covariates in the multivariable model. Standard errors of the ARD were derived from bootstrap methods using 1000 resamples of the data. Patients with missing data were excluded, the extent of missing data is shown in Supplementary Table S2. Sensitivity analyses were conducted to test robustness of the results; each model was adjusted for a risk score developed from UK Transplant Registry data for kidney transplants performed in the 5 years prior to the study recruitment period (2006 - 2011), rather than adjusting for individual confounding factors. This minimised the number of degrees of freedom in the models, and enabled checking for any missed comorbidity effects. All analyses were conducted using SAS® 9.4 (SAS Institute Inc, Cary, USA).

Ethics approval

East of England Research Ethics Committee (reference number 11/EE/0120).

Results

Baseline characteristics

Characteristics of the DDKT (n=1288) and LDKT (n=812) recipients, donors and transplants are shown in Table 1. These were consistent with UK Transplant Registry data for the study recruitment period.[19, 20] The demographics of recruited versus excluded patients were compared (Supplementary Table S3). There was a higher proportion of White patients in the recruited group compared with the excluded group, however there were no significant differences in age group, gender or type of transplant. Table 2 shows the prevalence of comorbidity in the study cohort at the time of transplantation. DDKT recipients had significantly higher rates of diabetes (16.0% vs 10.3%, p=0.0002), IHD (9.8% vs 7.0%, p=0.029), HF (3.1% vs 1.6%, p=0.033), CVD (5.8% vs 3.1%, p=0.004) and PVD (3.3% vs 1.7%, p=0.027) compared with LDKT recipients.

DDKT recipients

a) Transplant survival

Overall, there were 134 "transplant failures" (85 graft failures and 49 patient deaths). The Kaplan-Meier estimate for two-year transplant survival was 89.4% (95% confidence interval [CI] 87.6, 91.0). After adjustment for relevant factors in the multivariable Cox regression model, HF (HR 2.39, 95% CI 1.30, 4.37, p=0.005) and CVD (HR 2.33, 95% CI 1.40, 3.88, p=0.001) were associated with a significant increase in the risk of transplant failure (Table 3). There was no significant inter-centre variation in transplant survival when including transplant centre as a random effect in the model (difference in -2LogL=0.02, degrees of freedom [df]=1, p=0.885). For HF, the ARD was 0.117 (standard error [SE] 0.052) (i.e.

patients with heart failure had an 11.7% increased risk of transplant failure within 2 years compared to those without heart failure, after adjustment for all other factors in the multivariable model). For CVD, the ARD was 0.101 (SE 0.043). The effect of adding DGF to the final model is shown in Supplementary Table S4.

b) Graft survival

At two years, there were 85 graft failures, and the Kaplan-Meier estimate of graft survival was 93.2% (95% CI 91.7, 94.5). Multivariable Cox regression modelling showed PVD (HR 3.04, 95% CI 1.37, 6.74, p=0.006) and obesity (BMI ≥30.0) (HR 2.27, 95% CI 1.27, 4.06, p=0.006, compared with normal BMI 18.5 – 24.9) to be independent risk factors for graft loss (Table 3). The obesity variable was explored further in the model by dividing it into class I and class II and above (BMI 30.0 – 34.9 and ≥35.0 respectively) (Supplementary Table S5). There were too few patients with obesity class III (BMI ≥40.0) (n=7) to include this as a separate category. There was no significant variation in the risk of graft failure for the different classes of obesity, therefore the broader category of obesity (BMI ≥30.0) was retained in the main model (Table 3). No centre effect on graft survival was found when modelling centre as a random effect (difference in -2LogL=0.23, df=1, p=0.632). Among patients with PVD, the risk of graft failure was highest in the first ten days following transplantation, as demonstrated by the initial steep drop in the survival curve before the more gradual decline (Figure 2A); 85.7% graft failures in the PVD group occurred during this early post-operative period, compared with 26.9% among patients without PVD. In contrast, the impact of obesity on graft survival followed a more gradual decline over the two-year period (Figure 2B). Unadjusted two-year graft survival estimates for patients with and without PVD and obesity are shown in Table 4. The ARD for PVD was 0.104 (SE 0.058) and for obesity was 0.060 (SE 0.029). The incidence of delayed graft function was 31.1% for all

patients, 48.7% for patients with PVD and 39.1% for patients with obesity. Adding DGF to the final model resulted in a reduction in the effect of PVD (Supplementary Table S4). The cause of graft failure for all patients as well as patients with PVD and obesity in the DDKT cohort is shown in Table 5.

c) Patient survival

There were 56 patient deaths, of which 49 were deaths with a functioning graft. The two-year Kaplan-Meier survival estimate was 95.4% (95% CI 94.1, 96.5). The comorbidities significantly associated with inferior patient survival in the multivariable model included HF (HR 3.77, 95% CI 1.79, 7.95, p=0.0005), CVD (HR 3.45, 95% CI 1.72, 6.92, p=0.0005) and CLD (HR 4.36, 95% CI 1.29, 14.71, p=0.018) (Table 3). There were no significant centre differences in patient survival (difference in -2LogL=0.01, df=1, p=0.925). Among patients with HF and CVD, just over half of patient deaths occurred in the second year after transplantation (55.6% and 58.3% respectively), while 100% of deaths among patients with CLD occurred within the first year post-transplantation. This is demonstrated by the survival curves in Figures 3A, 3B and 3C. Unadjusted 2-year patient survival estimates for patients with and without HF, CVD and CLD are shown in Table 6. For HF, CVD and CLD the ARD was 0.159 (SE 0.057), 0.041 (SE 0.027) and 0.056 (SE 0.091) respectively. The effect of adding DGF to the final model is shown in Supplementary Table S4.

LDKT recipients

In the LDKT cohort it was only possible to model transplant survival, as the smaller number of recipients and outcome events prevented meaningful analysis of separate graft and patient survival models. There were 42 “transplant failures” (26 graft failures and 16 patient deaths). The Kaplan-Meier estimate for transplant survival at 2 years was 94.7% (95% CI 92.9, 96.0).

The multivariable model demonstrated significantly higher risk of transplant failure for HF (HR 3.83, 95% CI 1.15, 12.81, p=0.029) and diabetes (HR 2.23, 95% CI 1.03, 4.81, p=0.042) (Table 7). There was no significant centre effect on LDKT transplant survival (difference in -2LogL=0.11, df=1, p=0.741). The ARD for HF was 0.121 (SE 0.099) and for diabetes was 0.056 (SE 0.036).

Sensitivity analyses

Each multivariable model was checked by adjusting for a risk score (Supplementary Boxes S1, S2, S3 and S4) rather than entering the confounding factors individually into the model (Supplementary Tables S6, S7, S8 and S9). No additional comorbidities were identified as significant, and hazard ratios were very similar to the original models, confirming the reliability of the results.

Discussion

In this national observational study, we have collected data prospectively on a wide range of comorbid conditions and identified those that predict poorer survival outcomes after kidney transplantation. Among DDKT recipients, PVD and obesity were associated with a two- to three-fold increased risk of graft failure within two years of transplantation, while the risk of death was three- to four-fold higher with HF, CVD and CLD. For LDKT recipients, HF and diabetes were associated with significant detrimental effects on overall transplant survival, but longer follow up is required to determine the separate effects on graft and patient survival.

Among DDKT recipients, a history of PVD increased the risk of graft failure by 10.4% after adjusting for confounding factors, with the majority of graft failures occurring in the early post-operative period. PVD is typically diagnosed clinically by measuring the ankle-brachial pressure index (ABPI), and our results are in agreement with a US study of 819 patients which reported a 2.77 times increased risk of graft failure for patients with a low ABPI (<0.9).[21] Pre-existing PVD affecting the aorta or iliac arteries may complicate implantation of the kidney graft, resulting in difficult anastomoses, cholesterol emboli or hypoperfusion of the graft, and subsequent failure in the early post-operative period.[22, 23] Our data showed a high incidence of technical operative issues as the cause of graft failure among PVD patients (42.9%). We also found that the addition of DGF to the regression model for DDKT graft survival reduced the effect of PVD and is thus a potential mediator of this effect. Despite being a high risk group, patients with PVD still derive a significant survival benefit from transplantation compared with dialysis.[24, 25] As such, a history of PVD should not preclude

transplantation, but given the high risk of early complications, appropriate pre-operative planning and informed consent of patients is crucial.

Obesity is an ongoing topic of controversy with regard to patient suitability for kidney transplantation. Some centres do not exclude patients with obesity, while others restrict access to the waiting list at specific BMI thresholds, which may differ considerably between centres, and even between clinicians within the same centre.[26] Despite conflicting outcomes from early single centre studies, more recent meta-analyses have confirmed the detrimental effect of obesity on graft survival.[27-30] Our results are in keeping with this evidence; with obesity conferring a 6% increased risk of graft failure among DDKT recipients. The mechanisms for this are unclear. There was a high incidence of acute rejection as a cause of graft failure among obese patients (44%) and this could be a potential cause for the higher risk of graft failure associated with obesity. Difficulties in achieving and maintaining the narrow therapeutic target concentrations of immunosuppressive drugs in obese patients have previously been reported.[31]

We found that HF was associated with a 15.9% higher risk of mortality after DDKT and 12.1% higher risk of transplant failure after LDKT. We acknowledge that in patients on dialysis, it can be difficult to make a clear distinction between HF and fluid overload; however, our findings demonstrate that a diagnosis of heart failure in the patient's record predicts poorer survival, irrespective of how the diagnosis was made or the exact pathophysiology. It is also noteworthy that although HF was identified as a significant risk factor, no effect was observed for IHD. Our findings concur with the results of a US study which found that pre-transplant impaired left ventricular systolic function (on single photon emission computed tomography (SPECT)) was associated with a significantly higher risk of

both cardiac mortality and all-cause mortality after kidney transplantation, while cardiac ischaemia (on SPECT) was not.[32] Our findings suggest that either IHD does not increase the risk of death within two years post-transplantation, or that current risk stratification of patients with IHD in the UK is effective.

CVD was associated with a 4.1% elevated risk of death among DDKT recipients. It is known that patients with ESRD have more severe carotid atherosclerosis than the general population and are at substantially greater risk of stroke.[33-35] A large US registry analysis demonstrated that transplantation reduced the risk of cerebrovascular events from 11.8% to 6.8% compared to patients remaining on the waiting list.[36] However, previous CVD remains a strong risk factor for further post-transplantation events and mortality.[35, 37, 38] Post-transplantation cerebrovascular events are associated with high mortality,[39] which is worse for haemorrhagic strokes (48%) compared with ischaemic strokes (6%).[38] In a prospective randomised controlled trial including 1652 kidney transplant recipients (ALERT trial), the use of Fluvastatin did not reduce the incidence of cerebrovascular events or mortality.[38] Further trials are needed to assess the ability of therapies to reduce the risk of further cerebrovascular events and mortality in this high risk population.

CLD was independently associated with 5.6% increased risk of mortality within two years of DDKT. There is a paucity of published research regarding CLD in kidney transplant outcomes. Previous studies have focussed on the role of hepatitis B and C related liver disease as predictors of increased mortality after kidney transplantation.[40-42] The present study is the first to demonstrate that CLD of any aetiology leads to reduced survival after DDKT. Further research is required to understand the underlying mechanisms.

Interestingly, a diagnosis of diabetes was identified as a risk factor for transplant failure among LDKT recipients, but not for DDKT recipients. The reason for this finding is unclear. Diabetes is a well-recognised risk factor for mortality after transplantation, primarily due to elevated cardiovascular risk.[43] It may be that this cardiovascular risk was actually accounted for by other comorbidity variables in the models for DDKT recipients, while in the LDKT cohort with a significantly lower prevalence of other comorbidities, diabetes may have served as more general marker of poorer outcomes. A recent large population cohort study in Australia and New Zealand demonstrated that patients with Type 2 diabetes had significantly poorer survival after kidney transplantation, with the highest risk being among younger patients under the age of 40 years.[44] In our study the LDKT population was significantly younger than the DDKT population and this may explain why diabetes was a significant risk factor in this population. The 5.6% higher risk of transplant failure among patients with diabetes (and 12% higher risk for patients with heart failure discussed previously) must be given due consideration in the context of LDKT, given the potential implications for both the recipient as well as the live donor.

A major strength of the present study is that it is a prospective and comprehensive analysis of a large cohort of transplant recipients from all UK transplant centres. The cohort included a large proportion of the national adult transplant population with a minimal amount of missing data, which adds to the reliability of the study. There are a number of limitations to this study. First, for practical reasons we used relatively broad definitions for each comorbidity and were unable to distinguish between differing levels of severity or duration for each condition. All comorbidity data were collected at the time of transplantation when patients were recruited to the study. Therefore, we were unable to assess the progression or improvement of each condition after transplantation, and whether this impacted on outcomes. Secondly, it should

be noted that the study population is largely of white ethnicity and thus conclusions with respect to other ethnic groups may be less certain. Thirdly, due to the favourable survival outcomes of LDKT recipients, we were only able to analyse the composite outcome of transplant survival in this cohort, as there were too few events for separate analysis of graft and patient survival. Transplant survival (also known as graft survival not censored for death) is a commonly analysed end-point in the transplant literature, as it demonstrates the overall success of a transplant.[45, 46] However, in the DDKT analysis we found that this method masked the importance of several comorbidity risk factors that were found to be significant when analysing graft and patient survival separately. Therefore, it is important that we carry out separate graft and patient survival analyses in the LDKT cohort after longer follow-up time. Finally, the results from this study describe associations and no causation can be inferred.

This study quantifies the risks associated with specific comorbid conditions in the context of kidney transplantation. The findings can be utilised in everyday clinical practice to fully inform patients of their individual risks and outcomes, to inform future wait-listing and allocation policy and also to guide further research into improving the outcomes of patients with specific comorbidities.

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Tables

Table 1. Characteristics of the study cohort

	DDKT recipients n=1288	LDKT recipients n=812	p-value
Recipient variables			
Recipient age, years (median, IQR)	54 (44 - 63)	46 (34 - 56)	<0.0001
Recipient age group, years (n, %)			<0.0001
18 – 34	132 (10.3)	229 (28.2)	
35 – 49	369 (28.7)	263 (32.4)	
50 – 64	543 (42.2)	252 (31.0)	
65 – 75	244 (18.9)	68 (8.4)	
Recipient gender (n, %)			0.267
Male	824 (64.0)	500 (61.6)	
Female	464 (36.0)	312 (38.4)	
Recipient ethnicity (n, %)			0.0002
White	1023 (79.7)	707 (87.1)	
Asian	140 (10.9)	62 (7.6)	
Black	96 (7.5)	35 (4.3)	
Other	25 (2.0)	8 (1.0)	
Primary renal disease (n, %)			<0.0001
Polycystic kidney disease	219 (17.0)	112 (13.9)	
Diabetic nephropathy	134 (10.4)	48 (5.9)	
Glomerulonephritis	320 (24.9)	232 (28.7)	
Pyelonephritis	138 (10.7)	128 (15.8)	
Hypertensive nephropathy	89 (6.9)	37 (4.6)	
Renal vascular disease	29 (2.3)	9 (1.1)	
Other	163 (12.7)	85 (10.5)	
Uncertain	194 (15.1)	157 (19.4)	
Time on dialysis (n, %)			<0.0001
Pre-emptive	137 (10.6)	279 (34.4)	
0 - 1 year	160 (12.4)	198 (24.4)	
1 - 3 years	366 (28.4)	185 (22.8)	
3 - 5 years	295 (22.9)	78 (9.6)	
> 5 years	330 (25.6)	72 (8.9)	
Previous transplant (n, %)	165 (12.9)	117 (14.5)	0.297
Highly sensitised, cRF≥85% (n, %)	126 (9.8)	95 (11.7)	0.163
Smoking status (n, %)			0.702
Non-smoker	137 (11.7)	78 (10.7)	
Ex-smoker	325 (27.7)	212 (29.2)	
Smoker	710 (60.6)	437 (60.1)	
Donor variables			
Donor age, years (median, IQR)	54 (43 - 64)	48 (39 - 57)	<0.0001
Donor age group, years (n, %)			<0.0001
<18	31 (2.4)	0	
18 – 34	160 (12.4)	143 (17.6)	
35 – 49	303 (23.5)	298 (36.7)	
50 – 64	512 (39.8)	308 (37.9)	
65 – 75	234 (18.2)	61 (7.5)	
>75	48 (3.7)	2 (0.3)	
Donor gender (n, %)			0.001
Male	696 (54.0)	379 (46.7)	
Female	592 (46.0)	432 (53.3)	
Donor ethnicity (n, %)			<0.0001
White	1208 (95.2)	720 (88.7)	
Asian	21 (1.7)	52 (6.4)	
Black	23 (1.8)	28 (3.5)	
Other	17 (1.3)	12 (1.5)	

Donor BMI, kg/m^2 (n, %)			<0.0001
Underweight (<18.5)	0	0	
Normal (18.5 - 24.9)	463 (37.3)	254 (32.9)	
Overweight (25.0 - 29.9)	494 (39.7)	390 (50.5)	
Obese (≥30.0)	286 (23.0)	128 (16.6)	
Transplant variables			
HLA MM level (n, %)			<0.0001
1	155 (12.0)	91 (11.2)	
2	355 (27.6)	105 (12.9)	
3	679 (52.7)	360 (44.3)	
4	99 (7.7)	256 (31.5)	
CIT, hours (median, IQR)	14.5 (11.4 - 17.3)	3.3 (2.4 - 4.1)	<0.0001
Delayed graft function (n, %)	378 (31.1)	30 (3.9)	<0.0001

DDKT; deceased-donor kidney transplant, LDKT; living-donor kidney transplant, IQR; interquartile range, cRF; calculated reaction frequency, BMI; body mass index, HLA MM; human leukocyte antigen mismatch, CIT; cold ischaemia time. Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Supplementary Table S2.

Table 2. Prevalence of recipient comorbidity

	DDKT recipients n=1288	LDKT recipients n=812	p-value
Diabetes (n, %)	205 (16.0)	83 (10.3)	0.0002
Ischaemic heart disease (n, %)	126 (9.8)	57 (7.0)	0.029
Heart failure (n, %)	40 (3.1)	13 (1.6)	0.033
Atrial fibrillation (n, %)	25 (1.9)	12 (1.5)	0.434
Cardiac valve replacement (n, %)	10 (0.8)	8 (1.0)	0.609
Pacemaker (n, %)	10 (0.8)	5 (0.6)	0.673
Cerebrovascular disease (n, %)	75 (5.8)	25 (3.1)	0.004
Peripheral vascular disease (n, %)	43 (3.3)	14 (1.7)	0.027
Abdominal aortic aneurysm (n, %)	4 (0.3)	2 (0.3)	0.790
Chronic respiratory disease (n, %)	108 (8.4)	59 (7.3)	0.359
Chronic liver disease (n, %)	25 (1.9)	14 (1.7)	0.722
Blood borne viruses (n, %)	38 (3.0)	13 (1.6)	0.051
Malignancy (n, %)	93 (7.2)	49 (6.1)	0.294
Mental illness (n, %)	75 (5.8)	41 (5.1)	0.453
BMI, kg/m^2 (n, %)			0.121
Underweight (<18.5)	26 (2.1)	23 (3.0)	
Normal (18.5 - 24.9)	461 (37.5)	312 (40.8)	
Overweight (25.0 - 29.9)	462 (37.6)	282 (36.9)	
Obese (≥30.0)	281 (22.9)	147 (19.2)	
Number of comorbidities (n, %)			0.002
0	573 (46.7)	414 (54.4)	
1 - 2	579 (47.2)	316 (41.5)	
≥3	74 (6.0)	31 (4.1)	

DDKT; deceased-donor kidney transplant, LDKT; living-donor kidney transplant, BMI; body mass index. Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Supplementary Table S2.

Table 3. Cox regression analysis for impact of comorbidity on 2-year survival outcomes of deceased donor kidney transplants

	Transplant survival model		Graft survival model		Patient survival model	
Variables	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Recipient comorbidity						
Heart failure	2.39 (1.30, 4.37)	0.005	-	-	3.77 (1.79, 7.95)	0.0005
Cerebrovascular disease	2.33 (1.40, 3.88)	0.001	-	-	3.45 (1.72, 6.92)	0.0005
Chronic liver disease	-	-	-	-	4.36 (1.29, 14.71)	0.018
Peripheral vascular disease	-	-	3.04 (1.37, 6.74)	0.006	-	-
BMI, kg/m^2						
Underweight (<18.5)	-	-	0.86 (0.11, 6.49)	0.885	-	-
Normal (18.5 - 24.9)	-	-	1 (reference)		-	-
Overweight (25.0 - 29.9)	-	-	1.48 (0.84, 2.61)	0.180	-	-
Obese (≥30.0)	-	-	2.27 (1.27, 4.06)	0.006	-	-
Other variables						
Time on dialysis (years)						
< 3	1 (reference)		1 (reference)		1 (reference)	
≥ 3	2.08 (1.41, 3.08)	0.0002	1.84 (1.11, 3.04)	0.018	2.47 (1.36, 4.50)	0.003
Recipient age (per 10 years)	1.10 (0.92, 1.30)	0.290	0.84 (0.68, 1.05)	0.128	1.67 (1.23, 2.25)	0.0009
Recipient ethnicity						
White	1 (reference)		1 (reference)		-	-
Asian	0.67 (0.35, 1.29)	0.228	0.76 (0.35, 1.69)	0.504	-	-
Black	1.23 (0.68, 2.21)	0.495	1.52 (0.77, 3.02)	0.228	-	-
Other	0.37 (0.05, 2.63)	0.317	0.62 (0.08, 4.53)	0.636	-	-
Highly sensitised (cRF≥85%)	1.47 (0.87, 2.47)	0.153	2.22 (1.18, 4.19)	0.014	-	-
Donor age (per 10 years)	1.14 (0.99, 1.31)	0.066	1.23 (1.02, 1.48)	0.028	1.11 (0.89, 1.39)	0.349
HLA MM level						
1	1 (reference)		1 (reference)		1 (reference)	
2	1.18 (0.62, 2.27)	0.612	2.94 (1.08, 7.98)	0.035	0.40 (0.16, 1.01)	0.052
3	1.05 (0.57, 1.94)	0.866	2.25 (0.85, 5.93)	0.103	0.46 (0.21, 1.01)	0.051
4	1.25 (0.53, 2.93)	0.612	2.78 (0.81, 9.59)	0.106	0.66 (0.22, 2.01)	0.467
Cold ischaemia time (per hour)	1.04 (1.01, 1.08)	0.028	1.01 (0.97, 1.06)	0.568	1.04 (0.99, 1.10)	0.118

HR; hazard ratio, CI; confidence interval, BMI; body mass index, cRF; calculated reaction frequency, HLA MM; human leukocyte antigen mismatch.

Table 4. Kaplan-Meier estimates for 2-year graft survival of deceased-donor kidney transplants

Comorbidity	Survival (95% CI)	p-value
Peripheral vascular disease		0.006
No	93.6 (92.0, 94.8)	
Yes	83.5 (68.5, 91.8)	
BMI, kg/m^2		0.012
Normal (18.5 - 24.9)	95.2 (92.7, 96.8)	
Obese (≥30.0)	90.1 (85.9, 93.1)	

p-value is for log-rank test.

Table 5. Cause of graft failure among DDKT cohort

Cause of graft failure	All patients	Obese patients	PVD patients
Acute rejection	26 (34.2%)	11 (44.0%)	1 (14.3%)
Vascular thrombosis	6 (7.9%)	0 (0%)	1 (14.3%)
Technical operative issues	9 (11.8%)	3 (12.0%)	3 (42.9%)
Non-viable kidney	9 (11.8%)	3 (12.0%)	1 (14.3%)
Infection	1 (1.3%)	0 (0%)	0 (0%)
Recurrent primary renal disease	4 (5.3%)	0 (0%)	0 (0%)
Other	21 (27.6%)	8 (32.0%)	1 (14.3%)

Table 6. Kaplan-Meier estimates for 2-year patient survival after deceased-donor kidney transplantation

Comorbidity	Survival (95% CI)	p-value
Heart failure		<0.0001
No	96.0 (94.8, 97.0)	
Yes	75.8 (58.5, 86.7)	
Cerebrovascular disease		<0.0001
No	96.2 (94.9, 97.1)	
Yes	82.7 (71.5, 89.8)	
Chronic liver disease		0.003
No	95.7 (94.3, 96.7)	
Yes	83.6 (62.0, 93.5)	

p-value is for log-rank test.

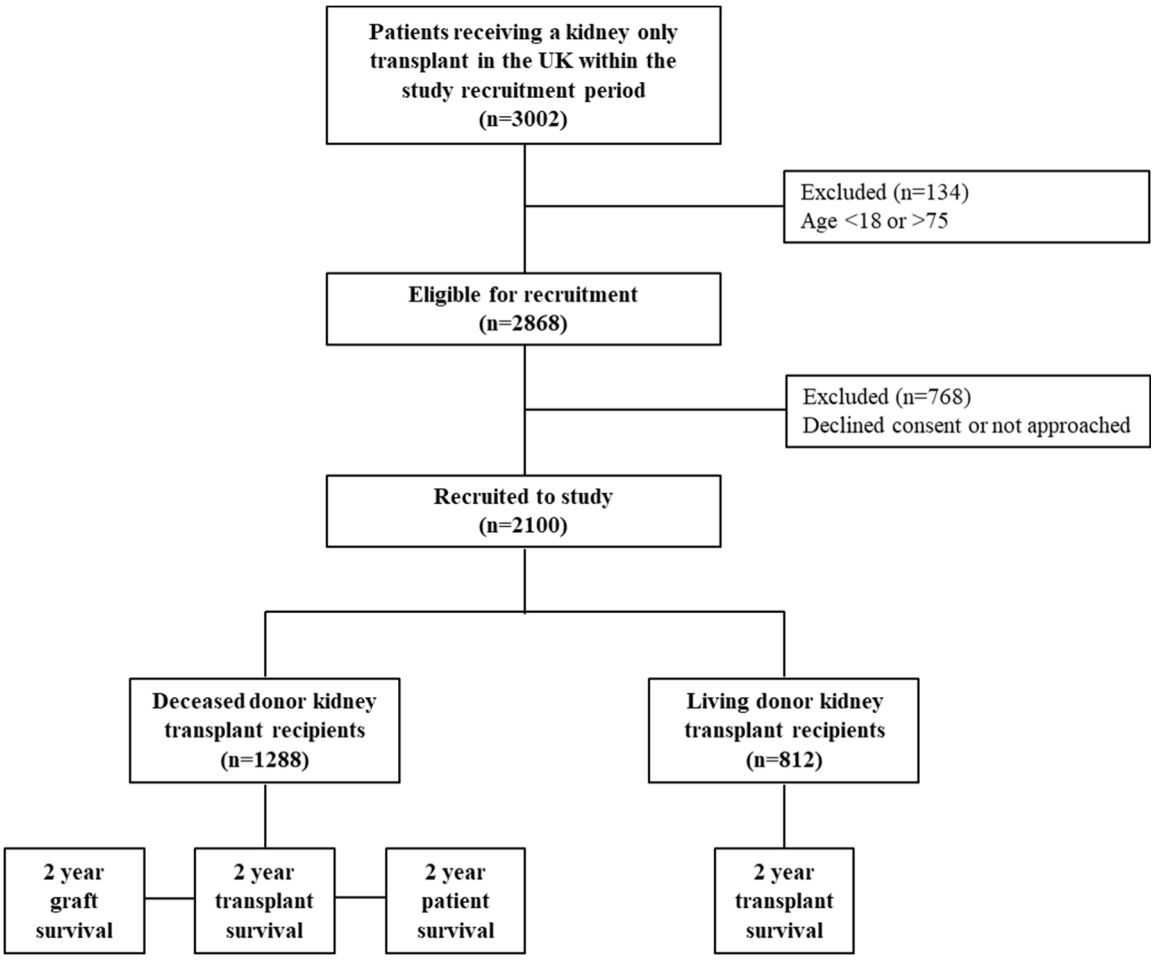
Table 7. Cox regression analysis for impact of comorbidity on 2-year transplant survival of living-donor kidney transplants

Variables	HR (95% CI)	p-value
Recipient comorbidity		
Heart failure	3.83 (1.15, 12.81)	0.029
Diabetes	2.23 (1.03, 4.81)	0.042
Other variables		
Time on dialysis (years)		
< 3	1 (reference)	
≥ 3	2.16 (1.13, 4.11)	0.019
Recipient age (per 10 years)	1.01 (0.80, 1.28)	0.926
Donor age (per 10 years)	1.03 (0.81, 1.31)	0.828
HLA MM level		
1	1 (reference)	
2	0.76 (0.23, 2.51)	0.657
3	0.74 (0.29, 1.86)	0.520
4	0.67 (0.25, 1.82)	0.428

HR; hazard ratio, CI; confidence interval, HLA MM; human leukocyte antigen mismatch.

Figures

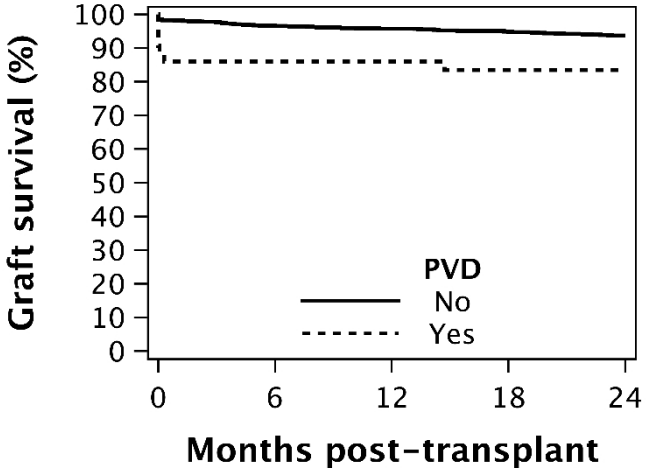
Figure 1. Study population and analyses



Patients were recruited from all 23 UK renal transplant centres. Recruitment took place over a 12-month period in each centre, between 1st November 2011 and 31st March 2013

Figure 2. Kaplan-Meier curves for 2-year graft survival of deceased-donor kidney transplants

A. Peripheral vascular disease (PVD)



B. Body mass index (BMI)

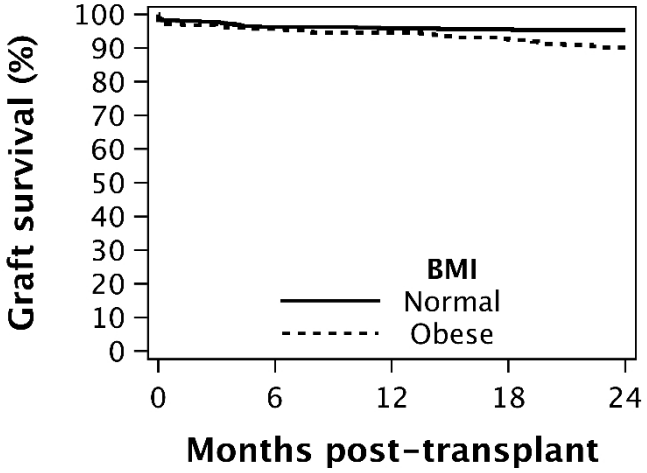
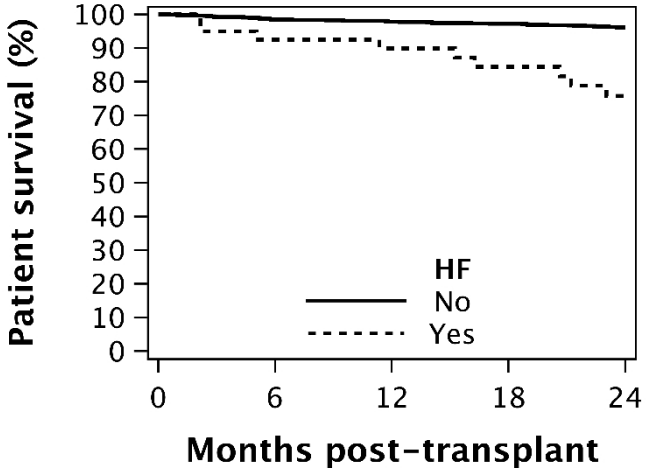
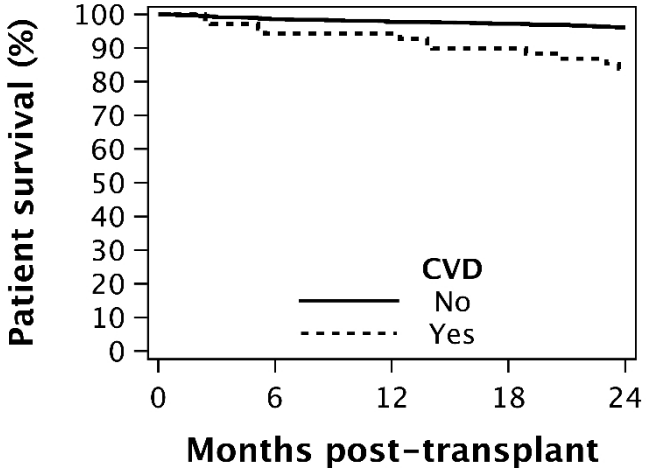


Figure 3. Kaplan-Meier curves for 2-year patient survival after deceased-donor kidney transplantation

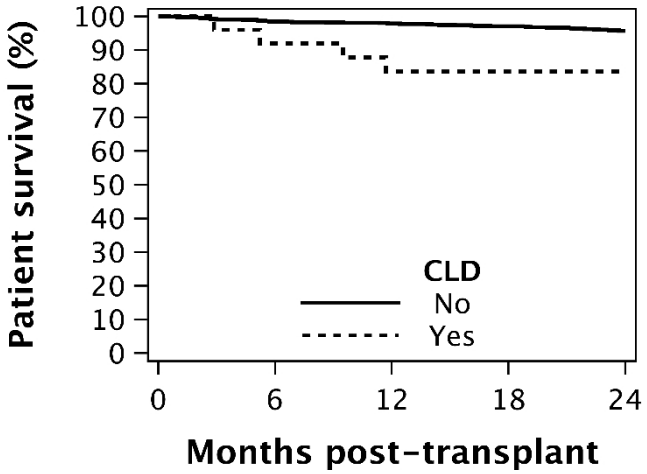
A. Heart failure (HF)



B. Cerebrovascular disease (CVD)



C. Chronic liver disease (CLD)



Supplementary Material

Table S1. Comorbidity variable definitions	
Comorbidity	**Definition (presence of any of the following)**
Diabetes	• Any cause of diabetes • Type I diabetes – Insulin required from time of diagnosis • Type II diabetes – Treatment with diet-control, oral antidiabetic medication or insulin
Ischaemic heart disease	• Angina – chest pain on exertion, relieved by rest or Glyceryl Trinitrate. As reported by patient or as documented in the case notes, with or without ECG changes, exercise tolerance testing or other imaging • Non-ST segment elevation myocardial infarction (NSTEMI) – troponin rise and non-ST segment elevation ischaemic ECG changes such as ST depression, T-wave inversion or no ECG changes. • ST segment elevation myocardial infarction (STEMI) – troponin rise and ST segment elevation on ECG. • Percutaneous coronary intervention (coronary angioplasty with or without stent insertion) • Coronary artery bypass graft operation
Heart failure	• Congestive cardiac failure • Left ventricular failure • Right ventricular failure • Left or right ventricular dysfunction on cardiac echo • Ejection fraction <30% on cardiac echo
Atrial fibrillation	• Patients in chronic atrial fibrillation at the time of recruitment, previous isolated episodes not included
Cardiac valve replacement	• Any kind of cardiac valve replacement or repair
Pacemaker	• Permanent pacemaker in-situ

Cerebrovascular disease	• Transient ischaemic attack (TIA) – also known as “mini-stroke”. Transient episode of neurologic dysfunction caused by ischaemia without infarction. Symptoms typically lasting less than 24 hours.
	• Cerebrovascular accident (CVA) including:
	  o Ischaemic stroke
	  o Cerebral haemorrhage
	  o Subarachnoid haemorrhage
	  o Subdural haemorrhage
	• Previous carotid intervention including:
	  o Carotid endarterectomy
	  o Carotid angioplasty

Peripheral vascular disease	• Claudication – lower limb pain on walking as reported by the patient, with or without doppler or angiographic evidence.
	• Radiological diagnosis
	• Radiological or surgical intervention including:
	  o Angioplasty
	  o Endarterectomy
	  o Bypass graft
	  o Amputation of any part of limb

Abdominal aortic aneurysm	• Radiological diagnosis under surveillance • Previous endovascular aneurysm repair • Previous open surgical repair
Chronic respiratory disease	• Any kind of chronic respiratory disease including: • Asthma – inflammatory condition of the lungs causing recurrent attacks of breathlessness and wheezing, differs in severity and occurs in all age groups. • Chronic obstructive pulmonary disease (COPD) – chronic and progressive airflow obstruction that is not fully reversible. FEV1/FVC ratio <0.7 and FEV1 < 80% predicted.

	• Bronchiectasis – abnormal and irreversible dilatation of the bronchi due to destruction of elastic and muscular tissue by acute or chronic inflammation and infection. Results in chronic infections and airway obstruction.
Chronic liver disease	• Persistent enzyme evidence of hepatic dysfunction with imaging or biopsy evidence of cirrhotic or non-cirrhotic liver disease • Excludes cholecystitis or gallstones
Blood borne viruses	• Hepatitis C • Hepatitis B • HIV
Malignancy	• Diagnosis of any malignancy in the past or in the present. Does not include benign tumours such as breast adenoma, colon polyp, actinic keratosis etc.
Mental illness	• Any diagnosis of mental illness e.g. depression, psychosis, bipolar disorder, substance abuse, deliberate self-harm, schizophrenia

Data for comorbidities were extracted from patient case notes, local electronic patient information systems and/or confirmed with the patients named consultant nephrologist at the time of recruitment to ATTOM.

Table S2. Missing data		
Variables	**DDKT recipients n=1288**	**LDKT recipients n=812**
Recipient variables		
Recipient age	0	0
Recipient gender	0	0
Recipient ethnicity	4 (0.31%)	0
Primary renal disease	2 (0.16%)	4 (0.49%)
Time on dialysis	0	0
Previous transplant	7 (0.54%)	4 (0.49%)
Sensitisation level	0	0
Smoking status	116 (9.0%)	85 (10.5%)
Donor variables		
Donor age	0	0
Donor gender	0	1 (0.12%)
Donor ethnicity	19 (1.48%)	0
Donor BMI	45 (3.49%)	40 (4.93%)
Transplant variables		
HLA MM level	0	0
CIT (per hour)	17 (1.32%)	66 (8.13%)
Recipient comorbidity variables		
Diabetes	3 (0.23%)	2 (0.25%)
Ischaemic heart disease	3 (0.23%)	2 (0.25%)
Heart failure	2 (0.16%)	2 (0.25%)
Atrial fibrillation	2 (0.16%)	2 (0.25%)
Cardiac valve replacement	3 (0.23%)	4 (0.49%)
Pacemaker	2 (0.16%)	3 (0.37%)
Cerebrovascular disease	2 (0.16%)	3 (0.37%)
Peripheral vascular disease	2 (0.16%)	3 (0.37%)
Abdominal aortic aneurysm	2 (0.16%)	3 (0.37%)
Chronic respiratory disease	2 (0.16%)	2 (0.25%)
Chronic liver disease	2 (0.16%)	2 (0.25%)
Blood borne viruses	3 (0.23%)	2 (0.25%)
Malignancy	2 (0.16%)	2 (0.25%)
Mental illness	2 (0.16%)	2 (0.25%)
BMI	58 (4.50%)	48 (5.91%)
Outcome variables		
Delayed graft function	74 (5.7%)	49 (6.0%)
Graft survival	2 (0.16%)	3 (0.37%)
Patient survival	1 (0.08%)	3 (0.37%)
Cause of graft failure	9 (10.58%)	2 (7.69%)

DDKT; Deceased-donor kidney transplant, LDKT; Living-donor kidney transplant, BMI; body mass index, CIT; cold ischaemia time.
Data are number (%).

Table S3. Demographics of excluded vs recruited kidney transplant recipients

Variable	Excluded (%)	Recruited (%)	p-value
Age group			0.307
18 – 34	15.5	17.2	
35 – 49	29.0	30.1	
50 – 64	38.0	37.9	
65 – 75	17.4	14.9	
Gender			0.332
Male	61.1	63.0	
Female	38.9	37.0	
Ethnicity			0.001
White	76.0	82.4	
Asian	13.5	9.6	
Black	7.4	6.2	
Other	2.3	1.6	
Missing	0.7	0.2	
Type of transplant			0.253
LD	36.3	38.7	
DD	63.7	61.3	

Table S4. Cox regression analysis for impact of comorbidity and delayed graft function on 2-year survival outcomes of deceased donor kidney transplants

	Transplant survival model		Graft survival model		Patient survival model	
Variables	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Recipient comorbidity						
Heart failure	2.77 (1.50, 5.12)	0.001	-	-	3.86 (1.82, 8.20)	0.0004
Cerebrovascular disease	2.05 (1.17, 3.59)	0.012	-	-	3.50 (1.73, 7.08)	0.0005
Chronic liver disease	-	-	-	-	4.68 (1.39, 15.79)	0.013
Peripheral vascular disease	-	-	2.58 (1.01, 6.59)	0.047	-	-
BMI, kg/m^2						
Underweight (<18.5)	-	-	1.52 (0.19, 11.67)	0.688	-	-
Normal (18.5 - 24.9)	-	-	1 (reference)		-	-
Overweight (25.0 - 29.9)	-	-	1.96 (1.01, 3.78)	0.046	-	-
Obese (≥30.0)	-	-	2.83 (1.43, 5.62)	0.003	-	-
Other variables						
Delayed graft function	1.75 (1.19, 2.56)	0.004	1.86 (1.12, 3.09)	0.017	1.24 (0.70, 2.20)	0.463
Time on dialysis (years)						
< 3	1 (reference)		1 (reference)		1 (reference)	
≥ 3	2.06 (1.35, 3.13)	0.0008	2.02 (1.15, 3.55)	0.014	2.26 (1.24, 4.15)	0.008
Recipient age (per 10 years)	1.06 (0.88, 1.28)	0.528	0.81 (0.64, 1.03)	0.086	1.56 (1.17, 2.15)	0.0003
Recipient ethnicity						
White	1 (reference)		1 (reference)		-	-
Asian	0.76 (0.39, 1.47)	0.418	0.88 (0.40, 1.96)	0.756	-	-
Black	0.83 (0.41, 1.67)	0.598	1.10 (0.49, 2.46)	0.826	-	-
Other	0.00 (0.00, 0.00)	.	0.00 (0.00, 0.00)	.	-	-
Highly sensitised (cRF≥85%)	1.52 (0.86, 2.67)	0.151	2.35 (1.16, 4.77)	0.018	-	-
Donor age (per 10 years)	1.09 (0.93, 1.27)	0.280	1.14 (0.93, 1.40)	0.208	1.07 (0.86, 1.35)	0.538
HLA MM level						
1	1 (reference)		1 (reference)		1 (reference)	
2	1.25 (0.61, 2.58)	0.544	3.95 (1.14, 13.72)	0.018	0.39 (0.15, 1.04)	0.059
3	1.15 (0.58, 2.27)	0.696	2.94 (0.86, 9.97)	0.084	0.51 (0.23, 1.16)	0.107
4	1.03 (0.38, 2.79)	0.951	2.19 (0.42, 11.42)	0.323	0.74 (0.24, 2.33)	0.608
Cold ischaemia time (per hour)	1.03 (0.99, 1.07)	0.105	1.02 (0.95, 1.06)	0.940	1.05 (0.99, 1.11)	0.102

HR; hazard ratio, CI; confidence interval, BMI; body mass index, cRF; calculated reaction frequency, HLA MM; human leukocyte antigen mismatch.

Table S5. Cox regression analysis for impact of BMI on 2-year graft survival of deceased donor kidney transplants

BMI (kg/m^2)	n	HR (95% CI)	p-value
Underweight (<18.5)	26	0.88 (0.11, 6.49)	0.885
Normal (18.5 - 24.9)	461	1 (reference)	
Overweight (25.0 - 29.9)	462	1.48 (0.84, 2.61)	0.180
Obese class I (30.0 - 34.9)	222	2.29 (1.23, 4.26)	0.009
Obese class II/III (≥35.0)	59	2.19 (0.87, 5.46)	0.094

Model adjusted for peripheral vascular disease, time on dialysis, recipient age, recipient ethnicity, highly sensitised (cRF≥85%), donor age, HLA MM level and cold ischaemia time.

Table S6. Cox regression model for 2-year transplant survival of deceased-donor kidney transplants (including risk score)

Variables	HR (95% CI)	p-value
Heart failure	2.38 (1.30, 4.34)	0.005
Cerebrovascular disease	2.21 (1.34, 3.67)	0.002
Time on dialysis (years)		
< 3	1 (reference)	
≥ 3	2.17 (1.49, 3.16)	<0.0001
Risk score (per unit)	1.11 (1.03, 1.19)	0.005

HR; hazard ratio, CI; confidence interval.
Model is adjusted for a risk score (Box S1) that incorporates relevant confounding variables.

Box S1. Risk score for 2-year transplant survival based on UK transplant registry data for deceased-donor kidney transplants in 2006 - 2011 (n=6469)

Transplant survival risk score = exp [- 0.3687 if recipient age 30-39
- 0.3885 if recipient age 40-49
- 0.2020 if recipient age 50-59
- 0.1863 if recipient age 60-64
+ 0.1589 if recipient age is 65-75
+ 0.1808 if recipient ethnicity Asian
+ 0.2745 if recipient ethnicity Black
- 0.5727 if recipient ethnicity Other
+ 0.2494 if recipient highly sensitised (cRF≥85%)
+ 0.02475 x donor age
- 0.2978 if HLA MM level 1
+ 0.1518 if HLA MM level 3
- 0.07197 if HLA MM level 4
+ 0.00613 x cold ischaemic time in hours]

exp; exponential function, HLA MM; human leukocyte antigen mismatch, cRF; calculated reaction frequency.
HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section). “Other” is any ethnicity other than White, Asian or Black.

Table S7. Cox regression model for 2-year graft survival of deceased-donor kidney transplants (including risk score)

Variables	HR (95% CI)	p-value
Peripheral vascular disease	2.74 (1.25, 5.99)	0.012
BMI, kg/m^2		
Underweight (<18.5)	0.97 (0.13, 7.23)	0.977
Normal (18.5 - 24.9)	1 (reference)	
Overweight (25.0 - 29.9)	1.33 (0.76, 2.34)	0.319
Obese (≥30.0)	2.14 (1.20, 3.80)	0.010
Time on dialysis (years)		
< 3	1 (reference)	
≥ 3	2.08 (1.29, 3.35)	0.003
Risk score (per unit)	1.21 (1.07, 1.37)	0.003

HR; hazard ratio, CI; confidence interval, BMI; body mass index. Model is adjusted for a risk score (Box S2) that incorporates relevant confounding variables.

Box S2. Risk score for 2-year graft survival based on UK transplant registry data for deceased-donor kidney transplants in 2006 - 2011 (n=5569)

Graft survival risk score = exp [- 0.5205 if recipient age 30-39
- 0.6398 if recipient age 40-49
- 0.5586 if recipient age 50-59
- 0.6910 if recipient age 60-64
- 0.4789 if recipient age is 65-75
+ 0.1503 if recipient ethnicity Asian
+ 0.2982 if recipient ethnicity Black
- 0.6247 if recipient ethnicity Other
+ 0.02813 x donor age
- 0.1626 if HLA MM level 1
+ 0.2599 if HLA MM level 3
- 0.06468 if HLA MM level 4
+ 0.00347 x cold ischaemic time in hours]

exp; exponential function, HLA MM; human leukocyte antigen mismatch. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section). “Other” is any ethnicity other than White, Asian or Black.

Table S8. Cox regression model for 2-year patient survival of deceased-donor kidney transplants (including risk score)

Variables	HR (95% CI)	p-value
Comorbidity		
Heart failure	3.72 (1.76, 7.87)	0.0006
Cerebrovascular disease	3.37 (1.69, 6.71)	0.0005
Chronic liver disease	3.94 (1.21, 12.83)	0.023
Time on dialysis (years)		
< 3	1 (reference)	
≥ 3	2.34 (1.30, 4.22)	0.005
Risk score (per unit)	1.02 (1.01, 1.03)	0.0009

HR; hazard ratio, CI; confidence interval.
Model is adjusted for a risk score (Box S3) that incorporates relevant confounding variables.

Box S3. Risk score for 2-year patient survival based on UK transplant registry data for deceased-donor kidney transplants in 2006 - 2011 (n=5569)

Patient survival risk score = exp [- 0.8798 if recipient age 30-39
+ 1.4404 if recipient age 40-49
+ 1.8680 if recipient age 50-59
+ 2.1586 if recipient age 60-64
+ 2.8002 if recipient age is 65-75
+ 0.01730 x donor age
- 0.4345 if HLA MM level 1
- 0.01808 if HLA MM level 3
- 0.1475 if HLA MM level 4
+ 0.01632 x cold ischaemic time in hours]

exp; exponential function, HLA MM; human leukocyte antigen mismatch. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section).

Table S9. Cox regression model for 2-year transplant survival of living-donor kidney transplants (including risk score)

Variables	HR (95% CI)	p-value
Comorbidity		
Heart failure	3.63 (1.10, 11.97)	0.035
Diabetes	2.21 (1.05, 4.66)	0.037
Other variables		
Time on dialysis (years)		
< 3	1 (reference)	
≥ 3	2.20 (1.16, 4.16)	0.016
Risk score (per unit)	1.02 (0.46, 2.23)	0.968

HR; hazard ratio, CI; confidence interval.
Diabetes includes any diagnosis of diabetes (both as a primary renal disease and a comorbidity).
Model is adjusted for a risk score (Box S4) that incorporates relevant confounding variables.

Box S4. Risk score for 2-year transplant survival based on UK transplant registry data for living-donor kidney transplants in 2006 - 2011 (n=3837)

Transplant survival risk score = exp [- 0.1519 if recipient age 30-39
- 0.2066 if recipient age 40-49
- 0.4011 if recipient age 50-59
- 0.05848 if recipient age 60-64
+ 0.3659 if recipient age is 65-75
+ 0.00879 x donor age
- 0.07066 if HLA MM level 1
- 0.01556 if HLA MM level 3
- 0.2242 if HLA MM level 4]

exp; exponential function, HLA MM; human leukocyte antigen mismatch. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section).