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Causes of renal allograft failure in the United Kingdom: trends in UK Renal Registry and NHS Blood and Transplant data from 2000–2013

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ABSTRACT

Background. Improvement in long-term renal allograft survival is impeded by incomplete or erroneous coding of causes of allograft loss. This study reports 13-year trends in causes of graft failure across the UK.

Methods. National Health Service Blood and Transplant (NHSBT) and UK Renal Registry data were linked to describe UK kidney patients transplanted 2000–2013. NHSBT graft failure categories were used, with 'other' recoded when free text was available. Adjusted analyses examined the influence of age, ethnicity and donor type on causes of graft failure.

Results. In 22,730 recipients, 5,389 (23.7%) grafts failed within a median follow-up of five years. The two most frequent causes were death with a functioning graft (40.8%) and alloimmune pathology (25.0%). Graft survival was higher in recipients who were younger (mean 47.3 vs. 50.7 years), received a pre-emptive transplant (20.2% vs. 10.4%), spent less time on dialysis (median 1.6 vs. 2.4 years) and received a living donor transplant (36.3% vs. 22.2%), with no differences by sex, ethnicity or human leukocyte antigen mismatch. Allograft failure within two years of transplantation fell from 12.5% (2000–2004) to 9.8% (2009–2013). Surgical and alloimmune related failures decreased over time while death with a functioning graft became more common. Age, ethnicity and donor type were factors in recurrent primary disease and alloimmune pathology.

Conclusions. Since 2000 there have been reductions in surgical and alloimmune graft failures in the UK. However, graft failure codes need to be revised if they are to remain useful and effective in epidemiological and quality improvement trials.

Keywords: epidemiology, graft failure, kidney transplant

INTRODUCTION

Allogeneic renal transplantation is the treatment of choice for end-stage kidney disease, offering superior outcomes in terms of morbidity and mortality when compared to dialysis [1, 2]. However, kidney transplants do not survive the lifespan of most recipients [3] and approximately 840 patients return to dialysis each year in the United Kingdom (UK) [4]. This makes allograft failure the fifth most common reason for people to start dialysis in the UK [5], while in the United States (US), allograft failure is the fourth most common reason [6].

Over the past decades there have unquestionably been great improvements in renal transplant survival in the first year post-transplantation [3]. However, there have not been similar improvements in outcomes beyond the first year. One of the major unmet needs in renal transplantation is to improve longer term allograft survival. A significant barrier to progress in this area is incomplete or erroneous understanding of the causes of longer term allograft loss.

Surprisingly few studies have reported causes of longer term graft loss, particularly for UK recipients. One large US study by El-Zoghby et al. [7] retrospectively analysed clinical and histological information for 1,317 kidney recipients, with a mean follow-up of 50 months. A quarter of grafts were lost over this time: 10.4% due to death with a functioning graft; 2.9% a result of primary non-function; and 11.6% due to death censored graft failure. This latter group was subdivided for cause: 36.6% glomerular diseases; 30.7% fibrosis/atrophy; 16.3% medical/surgical conditions; 11.8% acute rejection; and 4.6% unclassifiable. Glomerular pathologies included recurrent disease (23/56), transplant glomerulopathy (23/56) and presumed non-recurrent disease (10/56). Fibrosis/atrophy was only attributed to calcineurin inhibitor toxicity in one patient.

More recently, Sellarés et al. [8] prospectively studied 315 North American recipients after indication biopsies, 60 of whom progressed to graft failure at a median of 31.4 months. They undertook to explain each failure using biopsy diagnoses, human leukocyte antigen (HLA) antibody data and clinical information. Excluding four patients with missing information, failure was attributed to four main causes: 64.3% rejection; 17.9% glomerulonephritis; 7.1% polyoma virus nephropathy; and 10.7% intercurrent events. The heterogeneity of these data hints at the difficulties in assigning a precise cause for allograft

loss. However, differences in practice, for example in immune suppression regimens, mean that reasons for graft failure in the US cannot directly be extrapolated to Europe.

In this paper, we present outcome data for UK kidney recipients transplanted between 2000 and 2013. To date, this is the largest cohort of renal allograft losses reported worldwide and the first such study from the UK. This study forms a basis for future investigations and interventions to improve transplant outcomes.

MATERIALS AND METHODS

Study population

The study population included incident renal allograft recipients from 1 January 2000 to 31 December 2013, who met the following inclusion criteria: aged ≥18 years at the time of transplant; receiving a single organ transplant; receiving their first transplant; and transplanted at a UK renal centre reporting to the UK Renal Registry (UKRR) at the time of transplantation. The study population was restricted to those transplanted after 2000 because preliminary analysis of the entire National Health Service Blood and Transplant (NHSBT) dataset from 1983 established that the proportion of missing data prior to 2000 approached 40%. Patients were followed to 31 December 2014.

Dataset

Data were provided by both the UKRR and NHSBT; NHSBT data were linked to the patient cohort identified from UKRR data. This linkage ensured that all graft losses were captured, whether recorded as a lost graft or as a return to dialysis.

Revision of cause of graft failure categories

The historical NHSBT categories for causes of graft failure were as follows: hyperacute rejection; rejection whilst taking immunosuppressive drug(s); rejection after stopping all immunosuppressive drugs; recurrent primary renal disease; vascular or ureteric operative problems (excluding vascular thrombosis); vascular (arterial or venous) thrombosis; infection of graft; removal of functioning graft; non-viable kidney; other; and missing. We

deemed these categories insufficiently informative and to enable more meaningful reporting revised them as detailed in Box 1.

Refining the documented cause of graft failure

More than 600 graft losses were recorded by NHSBT as due to 'other' causes, with an accompanying free text entry supplied by the recipient's local renal unit. On reviewing the free text entries, it became apparent that a large number corresponded to more specific NHSBT coding categories. To improve the accuracy of the final dataset these losses originally recorded as 'other' were recoded independently by three researchers (HB, FC, RH). Any discrepancies were discussed amongst the study group until a consensus decision was reached. This process resulted in the reallocation of 59% of 'other' causes of graft loss to more specific graft failure categories. In addition, this process permitted the identification of common subcategories within 'other' (Box 1). These data provide an interesting insight into the range of pathological processes that can result in graft loss. In cases where the meaning of the free text was unclear, the cause of graft loss was assigned as 'other – miscellaneous'. Furthermore, the range of time to graft failure was examined within each category to highlight erroneous coding, for example, one graft failure >2,000 days post-transplant that had been coded as 'hyperacute rejection'.

Statistical analysis

Percentages were presented for categorical variables while medians and interquartile ranges were presented for the continuous variables not normally distributed. Means and standard variations were presented for continuous and normally distributed variables.

Analyses were based on the overall period of 2000–2013 as well as on separate cohorts 2000–2004, 2005–2008 and 2009–2013 to enable the investigation of trends. Data were censored at two years for some analyses comparing the cohorts, because some types of failure are more likely earlier than others and because the different cohorts have different durations of follow-up.

Multinomial logistic regression models were developed for the subgroup of patients whose grafts failed to identify the influence of patient specific variables including time to failure, transplant era, donor age, ethnicity, donor type and HLA mismatch on the probability of

having each cause of graft failure. All the models were adjusted for donor age, sex, primary renal disease (PRD) and ethnicity. These variables were clinically significant so we adjusted for them even in the case that they did not achieve statistical significance. The obtained predicted probabilities were presented in tables and graphs. There was a very low percentage of missing data and these were omitted from the statistical analyses, apart from missing data for the cause of graft failure which were categorised as 'missing'. P-values were only considered for pre-specified hypotheses to avoid multiple testing and identification of spurious associations.

All analyses were performed using SAS 9.3. The UKRR has permission from the Health Research Authority's Confidentiality Advisory Group (16/CAG/0064) and National Research Ethics Service (16/NE/0042) to use data collected without individual patient consent for research.

RESULTS

Study participants

A total of 22,730 recipients fulfilled the inclusion criteria and received a kidney transplant for the first time between 1 January 2000 and 31 December 2013. The median follow-up time was approximately five years. Three hundred and eighty-nine patients (1.7%) were lost to follow-up in the final dataset used for the cause of graft failure analysis. By the end of the follow-up period on 31 December 2014, a total of 5,389 allografts had failed, representing 23.7% of the study cohort (Figure 1).

As detailed in Table 1, those recipients whose allografts failed were noted to be older (mean age 50.7 vs. 47.3 years), to be less likely to have been transplanted pre-emptively (10.4% vs. 20.2%) or to have received a kidney from a living donor (22.2% vs. 36.3%) and were more likely to have spent longer on dialysis pre-transplant (median 2.4 vs. 1.6 years). However, no differences in sex, ethnicity or HLA mismatch were apparent. The spectrum of PRDs was also similar, although diabetic renal disease was more frequent in those with a failed allograft.

Causes of graft failure

As detailed in Figure 2, the most frequent cause of allograft failure in this UK cohort was death with a functioning graft, representing 40.8% of all grafts lost. The most common cause of allograft failure in surviving patients was alloimmune pathology, accounting for a further 25.0% of graft losses. Other recorded causes were surgical (8.2%); recurrent primary disease (3.5%); non-viable kidney (2.7%); infection of the graft (1.7%); and a variety of other pathologies listed in Box 1 (4.9%). Detailed information regarding these 'other' causes of graft loss are available as supplementary data (Table S1). No cause was recorded for 12.7% of failed allografts.

Causes of graft failure over time

Figure 3 depicts the total numbers of allografts lost at different time points post-transplantation and the trends in causes of graft loss over time. A clear difference can be seen between the first 12 months post-transplantation and subsequent years. As expected, surgical causes are more prominent in the early phase, together with non-viable kidney. After the first year, other causes including alloimmune pathology and death with a functioning graft become more prominent, but the relative contributions of these other causes then remain static over time.

To investigate whether trends in allograft failure have changed over time, the proportion of grafts failing within two years of transplant were compared for different transplant eras, as shown in Figure 4. This allows like-for-like comparison between the eras, which otherwise would have different durations of follow-up and therefore different causes of graft failure. Although the number of transplants performed has increased over time, the proportion of grafts failing in the first two years has fallen, from 12.5% of transplants carried out from 2000–2004, to 9.8% of transplants performed from 2009–2013. As not all centres reported to the UKRR prior to 2008, this analysis was repeated, limiting the data to those received from centres reporting in all three periods. Similar results were observed (data not shown).

On the background of this falling overall rate of graft loss by two years, it was also of interest to establish if the spectrum of causes of graft failure has changed over time (Figure 5). The most notable change is a reduction in the proportion lost due to alloimmune pathology and surgical cause in the most recent era, 2009–2013, mirrored by an increase in proportion lost due to death with a functioning graft. It is conceivable that this represents

improvements in immunosuppression regimes and surgical technique. Conversely, it may reflect more elderly patients with multiple comorbidities being transplanted between 2009 and 2013.

Demographical change over time

Table 2 explores the differences described above by detailing the demographics of the entire cohort according to transplant era. The number of transplants performed overall has increased over time. The age of recipients has increased slightly between the 2000–2004 and 2009–2013 cohorts (mean 46.1 vs. 49.8 years), as has donor age (45.6 vs. 48.4 years). As has been well documented elsewhere [9], donation after circulatory death (DCD) has steadily increased, with a corresponding reduction in the proportion of organs donated after brain death (DBD). Living donor transplantation increased substantially from 24.3% in 2000–2004 to 34.9% in 2005–2008 and continues to account for more than one third of transplants in the most recent transplant era. Pre-emptive transplantation also increased over time (11.2% to 21.0%). The proportion of patients from Asian and Black ethnic groups has also increased. In contrast, the spectrum of PRDs has remained largely constant.

Adjusted analyses

Several adjusted analyses were undertaken to assess the impact of recipient age, donor type and ethnicity on causes of allograft failure.

Table 3 details the spectrum of causes of allograft failure across different age categories after adjusting for sex, ethnicity and PRD. Even after adjusting for PRD, recurrent primary disease is more prominent as a cause of allograft failure in younger patients. This could be due to competing risks in older patients, who are less likely to lose their graft from recurrent disease. Alloimmune pathology is also more common in the younger age categories whilst, unsurprisingly, death with a functioning graft accounts for the largest proportion of allograft losses in the oldest age category.

Table 4 shows the impact of donor type on cause of allograft failure after adjusting for recipient age, sex and PRD. Recipients of a live donor kidney are more likely to have recurrent primary disease than patients receiving a kidney from a deceased donor, whilst

recipients of a DCD kidney are the most likely to lose their graft from a surgical cause. Beyond this, there is an equal distribution of causes across the other categories.

Table 5 indicates the causes of allograft failure in different ethnic groups after adjusting for recipient age, gender and PRD. Alloimmune pathology is more prominent in non-White patients, whilst death with a functioning graft is less likely in Black patients. The numbers are too small in the remaining categories of causes of graft loss to draw meaningful conclusions.

Figure 6 examines the impact of HLA mismatch on causes of allograft failure. The absolute numbers of graft failures by HLA mismatch and era are shown in Figure 7. As might be predicted, a lower proportion of alloimmune pathology is seen in patients with a 000 mismatch. These patients have a corresponding increase in death with a functioning graft.**Error! Reference source not found.**

DISCUSSION

Despite significant improvements in one-year kidney allograft survival, the rate of chronic graft loss beyond the first year remains substantial, with little improvement over the last decade [3]. Therefore, most kidney transplant recipients outlive their allografts and better long-term allograft survival remains a major unmet need in kidney transplantation. To address this issue requires a better understanding of the causes of long-term allograft loss.

In this paper, we have assessed allograft outcomes in over 20,000 UK kidney recipients transplanted in the modern era of immunosuppression. This includes the largest cohort of renal allograft losses so far reported and the only detailed analysis of the causes of renal allograft failure in Europe.

Risk factors for allograft failure

After a median follow-up of approximately five years, over 5,000 allografts had failed, which constituted almost one quarter of the study cohort. Risk factors for allograft failure included an older recipient, particularly those older than 55 years, longer time spent on dialysis, particularly time in excess of three years, and, unsurprisingly, receipt of a kidney from a deceased rather than a living donor. Patients transplanted pre-emptively had a lower likelihood of allograft failure (10.4% versus 20.2%). Interestingly, in this UK cohort there was

no impact of recipient sex, ethnicity or degree of HLA compatibility on the risk of allograft failure, although these are conventionally regarded as factors which influence long-term outcomes following kidney transplantation [10].

The changing causes of allograft failure over time

Overall, the two most frequent causes of allograft failure were death with a functioning graft, representing 40.8% of all grafts lost and alloimmune pathology, accounting for a further 25.0% of graft losses. We assessed trends in causes of graft loss over time, and, not unexpectedly, there is a clear difference in the principal causes of graft loss during the first six months post-transplantation, where surgical causes and non-viable kidney are prominent, and during subsequent years where other causes, including alloimmune pathology and death with a functioning graft, become more dominant. Beyond the first year after transplantation the proportion of grafts lost to any cause remains relatively constant. This may reflect the relatively short duration of follow-up in our study because it is reported elsewhere that, for example, recurrent glomerulonephritis after transplantation becomes more common with a longer follow-up period [11].

We also assessed trends in allograft failure across different transplant eras, focusing on the first two years after transplantation to enable like-for-like comparison. Reassuringly, the overall proportion of grafts failing within the first two years has fallen over time, from 12.5% of transplants performed between 2000 and 2004, to 9.8% of transplants performed between 2009 and 2013. Against this background, we observed a notable reduction in the proportion of grafts lost either due to alloimmune pathology or to surgical causes in the most recent era. These welcome trends are likely to reflect advances in surgical practice and changes in immunosuppressive protocols. However, they are mirrored by an increase in the relative proportion of grafts lost due to death with a functioning graft, which may reflect the increasing acceptance of elderly and co-morbid patients as transplant candidates.

To assess this further we explored the changing demographics of the entire patient cohort over time. While the overall number of transplants has increased, donor and recipient age has also increased. Donation after circulatory death has also steadily increased, with a corresponding reduction in the proportion of organs donated after brain death. We observed a substantial increase in the proportion of living donor kidney transplants, which

account for approximately one third of all kidney transplants in the most recent era. Rates of pre-emptive transplantation have increased, from 11.2% to 21.0%, and the proportion of non-White patients has also increased. There has been no change in the spectrum of PRDs.

Several adjusted analyses were undertaken to assess the impact of donor type, recipient age and ethnicity on the causes of graft failure. Unsurprisingly, there is a higher proportion of graft loss due to recurrent primary disease and to alloimmune pathology in younger patients, whereas older patients are more likely to die with a functioning graft. Recipients of a DCD kidney have the highest proportion of graft loss due to surgical causes, whilst recipients of a living donor kidney are more likely to lose their grafts due to recurrent primary disease than patients receiving a kidney from a deceased donor. This could be because living donors are often genetically related to the recipient and so the living donor kidney may be more sensitive to the underlying disease than an allograft from a deceased donor. Alloimmune pathology is more prominent in non-White patients, while death with a functioning graft is less likely in Black patients. As expected, a lower proportion of alloimmune pathology is seen in patients with a 000 HLA mismatch. These patients have a corresponding increase in death with a functioning graft.

Strengths and limitations

This study used a nationally comprehensive prospective cohort of kidney transplant recipients to investigate and describe trends in causes of graft failure. The same code list has been used throughout by NHSBT and a standardised approach was taken to combine these codes into new categories and review and code free-text causes of graft failure, where these were provided. Data were not available, however, on whether biopsies had been performed and whether the causes given were based on histology. It was also difficult to know how clinical teams had interpreted certain codes, such as rejection while taking versus after stopping immune suppression medication. We recognise that disease coding without clear description results in bias due to a tendency to follow ‘common wisdom’; the ease of selecting a predefined category can also hamper accurate data collection. Furthermore, the coding system does not allow for multifactorial graft loss, which is common in clinical practice. Lastly, the code list in use had not kept pace with developments in understanding of allograft immunology and pathology, such as chronic allograft damage due to interstitial fibrosis or tubular atrophy [12]. While we have cleaned and validated the UK cause of graft

failure as much as possible, we feel there is a real need to revise the code list. This might require the development of a new coding system, like the one developed by the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) for PRD [13]. Alternatively, it could be done using existing generic clinical terminology lists, such as Systematised Nomenclature of Medicine – Clinical Terms (http://www.snomed.org/snomed-ct), with back translation into groups of codes that are clinically relevant to nephrology. Further work needs to be done to shed more light on the causes of death in transplant recipients to identify ways to improve their long-term survival.

Although not the focus of this work, an additional limitation is the paucity of donor data available for analysis. Specific data regarding immunosuppression regimes is also unavailable.

CONCLUSION

We have presented a detailed analysis of allograft outcomes in a large, national cohort of UK kidney transplant recipients to assess the changing causes of renal allograft failure in the era of modern immunosuppression. We note that there are fewer early graft losses in the most recent cohort of patients and fewer allograft failures due to alloimmune and surgical causes. Death with a functioning graft remains the leading cause of allograft failure beyond the first six months following transplantation. While on the one hand this may reflect the increasing age of kidney transplant recipients, this may also suggest that there is scope for better modification of cardiac risk factors and improved management of cardiac and infectious disease in transplanted patients. If routine data are to support hypothesis generating observational analyses or efficient registry trials in the future, codes and definitions for core outcomes such as cause of graft failure need to be agreed and implemented.

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AUTHORS' CONTRIBUTIONS

Study concept and design: HB, FC, RH

Acquisition, analysis or interpretation of data: HB, LP, RS, RE, LM, KE, FC, RH

Drafting the manuscript: HB, LP, RS, RE, LM, KE, FC, RH

Critical revision of the manuscript for intellectual content: HB, LP, RS, RE, LM, KE, FC, RH

CONFLICT OF INTEREST STATEMENT

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

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TABLES

Box 1. Revised classification of causes of allograft failure

Original cause of graft failure categories	New cause of graft failure categories
Hyperacute rejection Rejection while taking immunosuppressive drug(s) Rejection after stopping all immunosuppressive drug(s) Other	Alloimmune pathology
Recurrent primary renal disease Other	Recurrent primary disease
Vascular or ureteric operative problems Vascular (arterial or venous) thrombosis Other	Surgical cause Thrombosis Vascular or ureteric operative problems (not thrombosis)
Infection of graft Other	Infection of graft
Removal of functioning graft Other	Removal of a functioning graft
Non-viable kidney Other	Non-viable kidney
Recipient died, graft still functioning at time of death	Death with a functioning graft
Other	Other >1 cause stated Acute kidney injury with non-recovery Acute tubular necrosis Biopsy related Calcineurin inhibitor toxicity De novo glomerulonephritis Donor pathology Drug related Hypertensive/ischaemic Infarcted kidney Interstitial fibrosis/tubular atrophy Interstitial nephritis Malignancy (graft) Malignancy (non-graft) Miscellaneous Mycotic aneurysm Patient death Post-transplant lymphoproliferative disease Pregnancy Primary non-function Thrombotic microangiopathy Transplant glomerulopathy
Missing	Missing

Table 1. Patient demographics for total follow-up time

Patient demographics	Total N=22,730	Surviving % or median (IQR) or mean (SD) N=17,341	Failed % or median (IQR) or mean (SD) N=5,389
Age at transplantation			
<40 years	6,585	30.1	25.4
40–54 years	8,473	39.3	30.8
≥55 years	7,672	30.6	43.8
Overall (mean [SD])	22,730	47.3 (13.3)	50.7 (14.4)
Recipient sex			
Male	13,978	61.3	62.3
Female	8,752	38.8	37.7
Recipient ethnicity			
Asian	2,268	10.1	9.7
Black	1,273	5.5	5.9
Other	469	2.2	1.5
White	18,714	82.2	82.9
Missing	6	0.0	0.0
Pre-transplant modality			
Haemodialysis	12,406	52.6	60.9
Peritoneal dialysis	6,226	27.0	28.6
Pre-emptive transplant	4,063	20.2	10.4
Unknown	35	0.2	0.2
Time on dialysis			
<1 year	8,070	38.8	24.8
1–3 years	7,252	31.3	33.9
>3 years	7,408	29.9	41.3
Overall (median [IQR])	22,730	1.6 (0.3–3.5)	2.4 (1.0–4.5)
Primary renal disease			
Diabetes	3,266	13.5	17.3
Glomerulonephritis	4,970	22.0	21.5
Hypertension	1,317	5.5	6.8
Missing	633	2.8	2.6
Other (high risk)	1,339	5.8	6.2
Other (low risk)	2,098	9.5	8.3
Polycystic disease	3,326	15.7	11.2
Pyelonephritis	2,259	9.9	10.0
Renal vascular disease	291	1.2	1.6
Uncertain	3,231	14.1	14.6
Donor type			
DBD	10,824	44.0	59.3
DCD	4,423	19.7	18.6
Live	7,483	36.3	22.2
Donor age			

<40 years	6,443	30.1	22.7
40–54 years	9,268	41.1	39.7
≥55 years	7,008	28.7	37.6
Missing	11	0.1	0.0
Overall (mean [SD])	22,719	46.2 (14.8)	49.6 (14.6)
HLA mismatch			
0 0 0	2,535	11.2	11.1
0DR & 0/1B	6,120	25.9	30.4
0DR & 2B or 1DR & 0/1B	9,606	42.5	41.6
1DR & 2B or 2DR	4,460	20.5	17.0
Missing	9	0.1	0.0
Cold ischaemic time (hours)			
Overall (median [IQR])	21,892	12.3 (3.5–16.9)	15.1 (9.8–19.3)
Missing	838		

IQR, interquartile range; SD, standard deviation; DBD, donors after brain death; DCD, donors after circulatory death; HLA, human leukocyte antigen

Table 2. Patient demographics by year of transplant for total follow-up time

Patient demographics	2000–2004		2005–2008		2009–2013	
	N=4,601	% or median (IQR) or mean (SD)	N=6,482	% or median (IQR) or mean (SD)	N=11,647	% or median (IQR) or mean (SD)
Age at transplantation						
<40 years	1,626	35.3	2,096	32.3	2,863	24.6
40–54 years	1,683	36.6	2,494	38.5	4,296	36.9
≥55 years	1,292	28.1	1,892	29.2	4,488	38.5
Overall (mean [SD])	4,601	46.1 (13.4)	6,482	46.6 (13.3)	11,647	49.8 (13.7)
Recipient sex						
Male	2,788	60.6	3,941	60.8	7,249	62.2
Female	1,813	39.4	2,541	39.2	4,398	37.8
Recipient ethnicity						
Asian	294	6.4	579	8.9	1,395	12.0
Black	159	3.5	360	5.6	754	6.5
Other	71	1.5	123	1.9	275	2.4
White	4,072	88.5	5,420	83.6	9,222	79.2
Missing	5	0.1	-		1	0.0
Pre-transplant modality						
Haemodialysis	2,291	49.8	3,518	54.3	6,597	56.6
Peritoneal dialysis	1,779	38.7	1,850	28.5	2,597	22.3
Pre-emptive transplant	516	11.2	1,102	17.0	2,445	21.0
Unknown	15	0.3	12	0.2	8	0.1
Time on dialysis						
<1 year	1,449	31.5	2,245	34.6	4,376	37.6
1–3 years	1,867	40.6	1,993	30.8	3,392	29.1
>3 years	1,285	27.9	2,244	34.6	3,879	33.3
Overall (median [IQR])	4,601	1.8 (0.8–3.2)	6,482	1.8 (0.5–4.0)	11,647	1.8 (0.3–3.8)
Primary renal disease						
Diabetes	583	12.7	992	15.3	1,691	14.5
Glomerulonephritis	1,083	23.5	1,385	21.4	2,502	21.5
Hypertension	256	5.6	330	5.1	731	6.3
Missing	55	1.2	104	1.6	474	4.1
Other (high risk)	279	6.1	376	5.8	684	5.9
Other (low risk)	356	7.7	619	9.6	1,123	9.6
Polycystic disease	693	15.1	931	14.4	1,702	14.6
Pyelonephritis	539	11.7	714	11.0	1,006	8.6
Renal vascular disease	57	1.2	82	1.3	152	1.3
Uncertain	700	15.2	949	14.6	1,582	13.6
Donor type						
DBD	3,178	69.1	3,173	49.0	4,473	38.4
DCD	305	6.6	1,049	16.2	3,069	26.4
Live	1,118	24.3	2,260	34.9	4,105	35.3
Donor age						
<40 years	1,421	30.9	1,963	30.3	3,059	26.3
40–54 years	1,954	42.5	2,772	42.8	4,542	39.0

≥55 years	1,221	26.5	1,743	26.9	4,044	34.7
Missing	5	0.1	4	0.1	2	0.0
Overall (mean [SD])	4,596	45.6 (14.5)	6,478	45.6 (14.6)	11,645	48.4 (15.0)
HLA mismatch						
0 0 0	591	12.9	781	12.1	1,163	10.0
0DR & 0/1B	1,880	40.9	1,584	24.4	2,656	22.8
0DR & 2B or 1DR & 0/1B	1,458	31.7	2,759	42.6	5,389	46.3
1DR & 2B or 2DR	667	14.5	1,354	20.9	2,439	20.9
Missing	5	0.1	4	0.1	-	
Cold ischaemic time (hours)						
Overall (median [IQR])	4,539	16.2 (9.5–20.2)	6,290	13.5 (3.2–17.9)	11,063	11.6 (4–16)
Missing	62		192		584	

IQR, interquartile range; SD, standard deviation; DBD, donors after brain death; DCD, donors after circulatory death; HLA, human leukocyte antigen

Table 3. Percentage distribution of causes of allograft failure according to recipient age group adjusted for sex (ref=male), PRD (ref=glomerulonephritis) and ethnicity (ref=White) for total follow-up time

Age group (yrs)	N	Alloimmune pathology (%)	Recurrent primary disease (%)	Surgical cause (%)	Infection of graft (%)	Removal of a functioning graft (%)	Non-viable kidney (%)	Death with a functioning graft (%)	Missing (%)	Other (%)
<40	1,339	39.4	14.6	8.1	0.8	0.1	1.2	11.2	20.4	4.2
40–54	1,616	27.4	8.9	8.2	0.9	1.1	2.1	31.4	16.0	4.1
≥55	2,291	15.8	4.9	6.9	0.6	0.8	2.8	52.5	12.0	3.7

Patients with missing data for PRD and ethnicity were excluded from the analysis

Table 4. Percentage distribution of causes of allograft failure according to donor type adjusted for recipient age group (ref=40–54 years), sex (ref=male), PRD (ref=glomerulonephritis) and ethnicity (White) for total follow-up time

Donor type	N	Alloimmune pathology (%)	Recurrent primary disease (%)	Surgical cause (%)	Infection of graft (%)	Removal of a functioning graft (%)	Non-viable kidney (%)	Death with a functioning graft (%)	Missing (%)	Other (%)
DBD	3,112	27.5	7.9	7.9	0.8	1.2	2.1	32.1	16.2	4.3
DCD	978	25.2	7.0	10.9	1.0	1.7	3.2	30.0	16.2	4.9
Live	1,156	28.2	12.6	7.3	1.1	0.5	1.4	30.4	15.4	3.2

Patients with missing data for PRD and ethnicity were excluded from the analysis

DBD, donors after brain death; DCD, donors after circulatory death

Table 5. Percentage distribution of causes of allograft failure according to ethnicity adjusted for recipient age group (40–54 years), sex (male) and PRD (glomerulonephritis) for total follow-up time

Ethnicity	N	Alloimmune pathology (%)	Recurrent primary disease (%)	Surgical cause (%)	Infection of graft (%)	Removal of a functioning graft (%)	Non-viable kidney (%)	Death with a functioning graft (%)	Missing (%)	Other (%)
White	4,344	27.4	8.9	8.2	0.9	1.1	2.1	31.4	16.0	4.1
Black	311	32.9	8.8	10.8	3.7	2.0	6.4	20.9	8.9	5.6
Asian	510	34.3	4.7	9.1	2.1	3.6	0.0	29.5	8.6	8.2
Other	81	34.4	4.6	9.0	4.0	2.4	5.0	25.0	10.8	4.9

Patients with missing data for PRD and ethnicity were excluded from the analysis

LEGENDS TO FIGURES

Figure 1. Flow diagram detailing allograft outcomes for the entire study cohort

Figure 2. Distribution of causes of allograft failure

Figure 3. Distribution of causes of allograft failure at different time points post-transplantation adjusted for recipient age group (40–54 years), sex (male), PRD (glomerulonephritis) and ethnicity (White)

Figure 4. Allograft failure within two years of transplantation across different transplant eras

Figure 5. Distribution of causes of allograft failure across different transplant eras adjusted for recipient age group (40–54 years), sex (male), PRD (glomerulonephritis) and ethnicity (White) for two years follow-up

Figure 6. Distribution of causes of allograft failure according to HLA mismatch adjusted for recipient age group (40–54 years), sex (male), PRD (glomerulonephritis) and ethnicity (White)

Figure 7. Number of allograft failures by HLA type and transplant era

Supplementary data

Table S1. Sub-categorisation of failed grafts coded as 'other'

Cause of graft failure	N	%
>1 cause stated	33	12.4
Acute kidney injury with non-recovery	39	14.7
Acute tubular necrosis	4	1.5
Biopsy related	1	0.4
Calcineurin inhibitor toxicity	5	1.9
De novo glomerulonephritis	2	0.8
Donor pathology	10	3.8
Drug related	1	0.4
Hypertensive/ischaemic	10	3.8
Infarcted kidney	7	2.6
Interstitial fibrosis/tubular atrophy	52	19.6
Interstitial nephritis	4	1.5
Malignancy (non-graft)	3	1.1
Miscellaneous	31	11.7
Mycotic aneurysm	3	1.1
Patient death	5	1.9
Post-transplant lymphoproliferative disease	8	3.0
Pregnancy	3	1.1
Primary non-function	42	15.8
Thrombotic microangiopathy	1	0.4
Transplant glomerulopathy	2	0.8
Total	266	100.0