

ORIGINAL ARTICLE

Death within the first year after kidney transplantation – an observational cohort study

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Summary

The risk of death within the first year postkidney transplantation is not well described in the contemporary era. We extracted data on all kidney transplant procedures performed in England between April 2001 and March 2012. Data linkage analysis was performed between Hospital Episode Statistics and the Office for National Statistics to identify all deaths. Cox proportional hazard models were performed to identify factors associated with 1-year mortality. 566 deaths (3.0%) occurred within the first year post-transplant (from 19 103 kidney transplant procedures analysed). Infection, cardiovascular events and malignancy were classified in 21.6%, 18.3% and 7.4% of death certificates, respectively. Among recipients with prior myocardial infarct history who died within the first year, 38.8% of deaths were attributed to a cardiac-related event. Malignancy-related death was responsible for 61.5% of 1-year mortality for allograft recipients with pretransplant cancer history. 22.1% of deaths included kidney failure as a contributory factor on the death certificate (3.3% specifically stated allograft failure). Variables associated with 1-year mortality included deceased-donor kidney, increasing age, residence in socioeconomically deprived area and history of select medical comorbidities pre-operatively. We conclude 1-year mortality postkidney transplantation is low, but in select allograft recipients, the risk of death increases considerably.

Introduction

Kidney transplantation is the gold-standard treatment for suitable individuals with end-stage kidney disease due to superior mortality outcomes [1]. However, any survival benefit is only realized after an early postoperative increased risk of death [2,3] and reinforces the importance of pretransplantation assessment appropriately selecting suitable candidates. Published guidelines stress the importance of pretransplantation work up to ensure survival of potential candidates is not compromised by transplantation [4,5]. This ensures allograft survival is not limited by premature death and attains maximum benefit from a limited resource. Therefore, death occurring within the first year post-transplant is an important audit measure for kidney transplant centres and a benchmark for acceptable practice.

The latest transplant activity report in the United Kingdom (from the NHS Blood and Transplant Service) reports excellent 1-year survival for patients who underwent their first kidney transplant between 2007 and 2010; 96% (donation after brain/cardiac death) and 99% (living kidney donation), respectively. Understanding risk factors and causality for death would allow targeted counselling of individualized risk/benefit ratio. There is a scarcity of information relating to cause of death within the first year of transplantation, contrary to increasing interest in long-term causes of death postkidney transplantation [6,7]. Gill and Pereira have previously reported 1-year mortality (4.6%) after kidney transplantation in a cohort dated between January 1995 and September 1997, with cardiac causes the most common cause of early mortality [8]. In the context of increasingly complex patients on kidney waiting lists [9],

determination of candidates at higher risk of death early post-transplant in the contemporary era will facilitate appropriate counselling and selection.

To inform clinical practice, we undertook a population-based cohort analysis of all deaths occurring within the first year postkidney transplantation in England since 2001 to determine causes, classifications and predictors of 1-year mortality. This was performed by data linkage analysis between Hospital Episode Statistics (for transplant procedures) and Office for National Statistics (for mortality) to ensure all deaths for all kidney transplant procedures were captured.

Material and methods

Study design

This was a retrospective, observational cohort study performed on prospectively registered national data sets. This study included all kidney transplant procedures (OPCS-4 codes; M01-M05, M08-M09) performed at any English kidney transplant centre (adult and paediatric) between April 2001 and March 2012. Combined organ transplants (kidney with another organ) were excluded from the analysis (n = 1,255). During this time period, 19 688 kidney transplant procedures were recorded in the HES data (635 recipients had repeat transplant performed during the 11-year period but only original transplant factored into survival analysis). 585 were excluded due to lack of completeness in relation to demographic information (age, gender or socioeconomic deprivation), leaving a final cohort of 19 103 recipients for analysis.

This study did not require institutional review board approval due to the pseudo-anonymized nature of the data retrieved – data were linked by NHS Informatics utilizing a special HES ID code and avoided patient identifiable codes. This observational study was registered with a clinical trials registry (NCT01798524). The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

Data sources

Data were obtained from Hospital Episode Statistics (HES), an administrative data warehouse containing admissions to all National Health Service hospitals in England [10]. Data extraction was facilitated utilizing codes on procedural classifications (Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th revision [OPCS-4]) [11] and medical classifications (World Health Organization International Classification of Disease, 10th revision [ICD-10]) [12].

With regard to outcome analysis, HES data alone have the limitation of only capturing deaths occurring in a hospital setting. Therefore, to obtain complete mortality data, the study cohort was cross-referenced with mortality data from the Office for National Statistics (ONS), which collects information on all registered deaths in the United Kingdom.

Study variables

Data were extracted from each kidney transplant procedure performed in England in relation to patient demographics at time of transplant; age, gender, donor type (living versus deceased), ethnicity (white, Black or Black British, Asian or Asian British, Chinese, mixed, other and unknown), allograft failure, medical comorbidities (acute myocardial infarct, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, connective tissue disorder, peptic ulcer, cancer, liver disease, diabetes mellitus) and socioeconomic deprivation (based upon Index of Multiple Deprivation [IMD] 2010). [13]. Data regarding allograft failure were defined using a surrogate marker in the absence of specific obtainable data (return to dialysis for ≥10 dialysis sessions beyond 90-days postkidney transplantation). These data were only obtainable for years from April 2006 onwards (11 961 kidney transplant procedures performed during this time period in England) and constituted supportive analysis for the Cox regression models.

Data quality

We adhered to the principles of the STROBE statement and have reported this article in accordance with recommended guidance [14]. In addition, we checked data accuracy from the HES database regarding transplant activity by corroborating HES data with the UK Transplant National Transplant database (where all transplant activity must be mandatorily reported). Transplant activity over the same dates as the study period was crosschecked between both databases to ascertain any discrepancy between data sets.

Classification of death

All deaths were classified into system-based categories. Two authors (DF, JC) converted all causes of death from ONS data from string to numerical data, with a third author independently verifying the data (AS). Any discrepancy on classification was resolved by discussion. Causes of death were classified under the following 12 categories; cardiovascular, cerebrovascular, vascular, infection, malignancy, trauma, renal, metabolic, gastrointestinal/liver, pulmonary, other and unknown.

Statistical methods

The primary outcome measure was mortality within the first year postkidney transplantation. SPSS (Version 20.0, Chicago, IL, USA) was utilized for data analysis unless otherwise stated. Normality of data was assessed using the Kolmogorov–Smirnov tests. Descriptive statistics were used to estimate the frequencies. Categorical variables are presented as number (%) and continuous variables as mean (±standard deviation) or median (±interquartile range) dependent upon normality of distribution. Difference between groups was assessed with chi-squared test or two-sided Fisher's exact test for categorical variables and *t*-test or Mann–Whitney *U*-test to compare continuous variables. A *P*-value less than 0.05 and 0.001 in the statistical analysis was considered significant and highly significant, tively.

Cox proportional hazard model in STATA (STATAcorp LP, College Station, TX, USA) (command stcox) was utilized. The proportionality assumption was checked for each variable and the whole model – for the main analysis, the proportionality assumption is true for all variables except cancer. Variables included in the model were age, gender, donor type (living versus deceased), socioeconomic deprivation, ethnicity (as classified by ONS), year of transplant and selected medical comorbidities (history of myocardial infarction, peripheral vascular disease, cerebrovascular disease, congestive cardiac failure pulmonary disease, liver disease, peptic ulcer, previous cancer and diabetes). Supportive analyses that included allograft failure in the model (defined as >=10 dialysis sessions from 90 days of the transplant) were performed to factor for this important variable – this was only possible for recipients transplanted from April 2006 onwards (n = 11,961).

With the assumption that data were missing at random, we simply performed listwise deletion and excluded the missing values from the analysis. Other missing data (e.g. ethnicity) were adjusted for as dummy variables in the models as required.

Results

A total of 19,688 kidney transplant procedures in England were recorded in the HES data for adult (18,499) and paediatric (n = 1,189) kidney allograft recipients – excluding those with missing demographic data (n = 585), we had a cohort of 19 103 for further analysis.

The median age for the whole cohort was 45 (interquartile range 34–55). 11 673 (61.1%) of the study cohort were male, with 7430 (38.9%) female. Ethnic breakdown of the study cohort comprised of white (13 695, 71.7%), Black or Black British (934, 4.9%), Asian or Asian British (1704, 8.9%), Chinese (81, 0.4%), mixed (166, 0.9%), other ethnic group (350, 1.8%) and unknown (2173, 11.4%). Socioeco-

nomic deprivation quintiles were (from most to least deprived, respectively); 1 (4203, 22.0%), 2 (4197, 22.0%), 3 (3765, 19.7%), 4 (3490, 18.3%) and 5 (3448, 18.0%). Living-donor transplantation occurred in 6262 (32.8%) of all kidney transplant procedures reported. Diabetes mellitus classification was the most common medical comorbidity recorded in 2968 (15.5%) of all kidney allograft recipients.

Data accuracy

Between April 2001 and March 2012, 19 405 kidney transplant procedures were registered with the UK National Transplant database (19 241 kidney alone, 49 en-bloc kidneys and 115 double kidneys transplants). This identifies a small discrepancy of 283 kidney transplant alone procedures that have been over-reported in the HES data in comparison with UK National Transplant Database records (concordance 98.6% between both data sets).

Mortality within first year postkidney transplantation

We identified 566 deaths that occurred within the first year postkidney transplantation over the last decade. The demographics of the cohort of kidney allograft recipients that died within the first year post-transplantation can be compared to the remaining transplant cohort in Table 1. From this comparative analysis, it can be observed that kidney allograft recipients that died within the first year after transplantation were more likely to be older, live in socioeconomically deprived areas, be recipients of deceased-donor kidneys and have a higher prevalence of pretransplantation medical comorbidities.

Age had a clear association for 1-year mortality with increasing risk of death as the age bracket of the allograft recipient increased; <50~(1.5%), 50–59~(3.8%), 60–69~(5.9%) and 70+~(11.8%), respectively. Supplementary Table 1 provides a comparative analysis comparing paediatric versus adult kidney allograft recipient deaths and demonstrates a significant difference in causality of death. Paediatric 1-year mortality was 0.6%, compared with 3.1% among adult kidney allograft recipients, and paediatric deaths were skewed towards traumatic, vascular and renal causes. South Asian allograft recipients had higher mortality within the first year post-transplantation compared to recipients of other ethnic groups (4.2% vs. 2.8%, respectively, P=0.001). There was no difference in mortality based upon gender (male versus female deaths, 3.0% vs. 2.9%, P=0.252).

Cause of death within first year postkidney transplantation

Figure 1 highlights cause of death within the first year postkidney transplantation based upon extrapolation of death

Table 1. Comparison of demographics between kidney allograft recipients alive versus deceased at 1 year post-transplantation.

Variable		Alive at 1 year	Death by 1 year	<i>P</i> -value
Numbers (percentage)		18 537 (97.0%)	566 (3.0%)	_
Age \pm standard deviation		44.2 ± 15.4	55.5 ± 13.3	< 0.001
Male sex		11 319 (61.1%)	354 (62.5%)	0.252
Ethnicity	White	13 302 (71.8%)	393 (69.4%)	0.083
	Black or Black British	908 (4.9%)	26 (4.6%)	
	Asian or Asian British	1633 (8.8%)	71 (12.5%)	
	Chinese	79 (0.4%)	2 (0.4%)	
	Mixed	164 (0.9%)	2 (0.4%)	
	Other	341 (1.8%)	9 (1.6%)	
	Unknown	2110 (11.4%	63 (11.1%)	
Social deprivation (IMD 2010)	1 (most deprived)	4058 (21.9%)	145 (25.6%)	0.052
	2	4065 (21.9%	132 (23.3%)	
	3	3665 (19.8%)	100 (17.7%)	
	4	3383 (18.2%)	107 (18.9%)	
	5 (least deprived)	3366 (18.2%)	82 (14.5%)	
Living-donor transplant		6181 (33.3%)	81 (14.3%)	< 0.001
History of myocardial infarct		454 (2.4%)	49 (8.7%)	< 0.001
History of congestive cardiac failure		105 (0.6%)	15 (2.7%)	< 0.001
History of cerebrovascular disease		258 (1.4%)	26 (4.6%)	< 0.001
History of peripheral vascular disease		139 (0.7%)	15 (2.7%)	< 0.001
History of pulmonary disease		899 (4.8%)	27 (4.8%)	0.505
History of connective tissue disease		376 (2.0%)	9 (1.6%)	0.292
History of peptic ulcer disease		65 (0.4%)	12 (2.1%)	< 0.001
History of liver disease		55 (0.3%)	6 (1.1%)	0.009
History of diabetes mellitus		2824 (15.2%)	144 (25.4%)	< 0.001
History of previous cancer		61 (0.3%)	13 (2.1%)	< 0.001

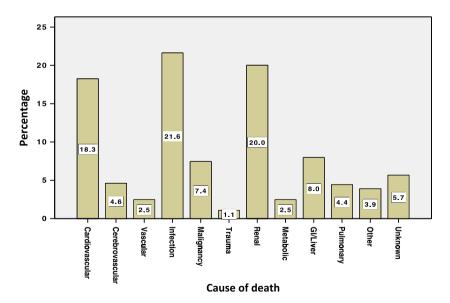


Figure 1 Cause of 1-year mortality after kidney transplantation in England between 2001 and 2012, based upon death certification to Office for National Statistics.

notification from ONS data. Infection was the most common cause of death (primary cause of death in 21.6% of death certificates). Cardiovascular disease and malignancy were the second most common causes of death, classified

in 18.3% and 7.4% of all death certificates, respectively. Causes of death within the first year were compared to causes beyond the first year postkidney transplantation for our study cohort (n = 1,521 deaths beyond first year), with

median follow-up 4.4 years (interquartile range 2.2-7.3 years). While infection, cardiovascular disease and malignancy remained the three most common cause of death they balanced up as equal causes of death after the first year post-transplantation; infection (n = 311, 20.4%), cardiovascular disease (n = 339, 22.3%) and malignancy (n = 334, 22.0%). Significant difference was observed in the overall profile of mortality comparing early (0-3 months) versus late (>3-12 months) deaths within the first year postkidney transplantation (Supplementary Table 2). For example, we observed infection and malignancy-related mortality to be more common beyond 3 months, while renal causes were more common within the first 3 months. In addition, we observed significant differences in the overall profile of mortality causality comparing the transplantation era 2001-2006 versus 2006-2012, respectively (Supplementary Table 3). Of particular interest was the observation that malignancy-related mortality was more common in the 2006-2012 versus 2001-2006 era (20.0% vs. 14.6%).

Select medical comorbidity risk factors were associated with predictably related mortality outcomes. For example, risk of death for recipients with pretransplant history of myocardial infarct was 9.7% vs. 2.8% for those with no relevant history (P < 0.001). Among recipients with prior

myocardial infarct history who died within the first year, 38.8% of deaths were attributed to a cardiac-related event. Risk of death for recipients with pretransplant history of congestive cardiac failure was 12.5% vs. 2.9% for those with no relevant history (P < 0.001). Among recipients with prior congestive cardiac failure history who died within the first year, 40.0% of deaths were attributed to a cardiacrelated event. Allograft recipients with prior cancer history had elevated risk of death within the first year postkidney transplantation versus recipient with no relevant history (17.6% vs. 2.9%, respectively, P < 0.001). Malignancyrelated death was responsible for 61.5% of 1-year mortality for allograft recipients with pretransplant cancer history. The three most common types of cancer leading to death postkidney transplantation were lymphoma (18.4%), lung (17.6%) and renal (9.8%). Finally, 6/13 deaths in kidney allograft recipients with known liver disease were of gastrointestinal/liver causes, compared to 124/2072 deaths in kidney allograft recipients without known liver disease (46.2% vs. 6.0%, respectively, P < 0.001).

Kidney allograft recipients with pretransplant history of diabetes demonstrated a higher risk for mortality after kidney transplantation compared to those without known diabetes (16.0% vs. 10.0%, respectively, P < 0.001). Cardiovascular causes were the most common cause of

Table 2. Cox Regression Proportional Hazard Model analysis of 1-year mortality postkidney transplantation.

Variable		Hazard ratio	Confidence interval	<i>P</i> -value
Age	<50	1.00		
	50–59	2.38	1.95–2.90	< 0.001
	60– 69	4.46	3.68-5.39	< 0.001
	70–79	7.62	5.84-9.94	< 0.001
	>=80	15.72	4.98-49.60	< 0.001
Female gender		1.01	0.86–1.17	0.920
Ethnicity	White	1.00	_	_
	Black/Black British	0.98	0.70-1.36	0.889
	Asian/Asian British	1.20	0.96-1.50	0.111
	Chinese	0.88	0.33–2.35	0.794
	Mixed	0.73	0.30-1.77	0.491
	Other	0.52	0.26-1.05	0.068
	Unknown	0.68	0.49-0.94	0.018
Socioeconomic deprivations (IMD 2010)	1 (most deprived)	1.00		
	2	0.84	0.68–1.05	0.124
	3	0.86	0.69-1.08	0.193
	4	0.86	0.68-1.08	0.190
	5 (least deprived)	0.60	0.46-0.77	< 0.001
Medical comorbidities	Acute myocardial infraction	1.52	1.15–2.01	0.003
	Congestive heart failure	1.51	0.77-2.93	0.229
	Peripheral vascular disease	1.70	1.17-2.47	0.006
	Cerebral vascular accident	1.66	0.91-3.03	0.097
	Liver disease	1.90	0.93-3.87	0.077
	Diabetes	1.64	1.38–1.93	< 0.001
	Cancer	2.27	1.27-4.07	0.006
Living-donor transplant		0.50	0.42-0.60	< 0.001
Allograft failure		2.70	1.75–4.19	< 0.001

death among diabetic recipients and significantly higher compared with nondiabetic recipients (4.2% vs. 2.0%, respectively, P < 0.001).

Concomitant allograft failure

124 (22.1%) deaths included kidney failure (however defined) as a contributory factor on the death certificate. Classifications that specifically documented allograft failure on the death certification were found in only 17 (3.3%) of deaths. Kidney failure (however defined) was more commonly documented on death certificates among allograft recipients who died from an infective episode versus other causes of death (27.4% vs. 19.7%, P = 0.028). No significant difference was observed between classification of kidney failure and other causes of death.

Survival and regression analysis for causes of 1-year mortality

Kaplan-Meier survival analysis was performed to assess unadjusted difference in risk of death within the first year

Case Processing Summary					
Live or deceased			Censored		
transplant	Total N	N of Events	N	Percent	
Deceased	12841	485	12356	96.2%	
Live	6262	81	6181	98.7%	
Overall	19103	566	18537	97.0%	

Overall Comparisons				
	Chi-Square	df	Sig.	
Log Rank (Mantel-Cox)	89.538	1	.000	

Test of equality of survival distributions for the different levels of Live or deceased transplant.

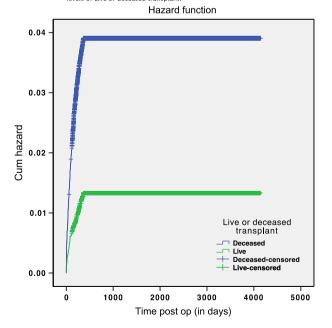


Figure 2 Kaplan–Meier hazard plot for risk of death at 1 year for living versus deceased-donor kidney transplant.

postkidney transplantation. Variables found to be associated with significant differences included living versus deceased-donor kidney (see Fig. 2 for hazard plot), age (see Fig. 3 for hazard plot), socioeconomic deprivation and selected medical comorbidities (e.g. diabetes mellitus and previous myocardial infarct etc.).

Cox proportional hazard models were performed to assess the impact of competing and confounding variables upon 1-year mortality. Acknowledging allograft failure as an important confounder, we devised a surrogate marker for allograft failure to incorporate into the Cox regression model. Variables found to be independently associated with increased mortality risk included increased age, higher socioeconomic deprivation, deceased-donor kidney, medical comorbidities and allograft failure (see Table 2). Removing allograft failure from the model retained similar results but reduced the impact of moderate socioeconomic

Case Processing Summary

			Censored	
Age2	Total N	N of Events	N	Percent
< 50	11421	166	11255	98.5%
50-59	4195	158	4037	96.2%
60-69	2887	171	2716	94.1%
70-79	589	70	519	88.1%
80+	11	1	10	90.9%
Overall	19103	566	18537	97.0%

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	364,450	4	.000

Test of equality of survival distributions for the different levels of Age2.

Hazard function

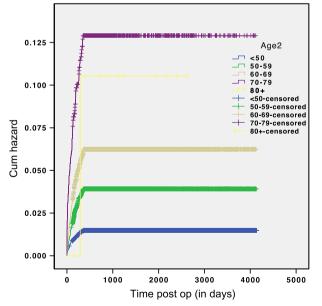


Figure 3 Kaplan–Meier hazard plot for risk of death at 1-year postkidney transplantation stratified by age groups (under 50, 50–59, 60–69, 70–79 and 80+, respectively).

deprivation quintiles on mortality, suggestive of some interaction. However, residence in most socioeconomically deprived areas retained a significant effect of patient mortality postkidney transplantation (hazard ratio 0.66, 95% CI 0.57–0.76, P < 0.001).

Discussion

This observational, cohort study is a comprehensive analysis of mortality within the first year postkidney transplantation in England. It confirms the independent association of perceived mortality risk factors that are commonly attributed to higher risk for death (e.g. age and diabetes) but also introduces hitherto unrecognised risk factors such as residence in socioeconomically deprived neighbourhoods. Infection, cardiovascular event and malignancy are the leading causes of death within the first year and correspond to pretransplantation risk factors. The results of this study can aid clinicians with appropriate selection and counselling of patients with end-stage kidney disease with regard to their short-term mortality risk after a kidney transplant.

This study complements previous work in this area highlighting increased mortality immediately postkidney transplantation. Gill and Pereira previously reported a 1-year mortality rate of 4.6% after kidney transplantation (cohort transplanted between January 1995 and September 1997), and it is interesting to observe our data have relatively similar overall and specific causes of death [8]. Both studies also share many risk factors for 1-year mortality, despite the two studies being over a decade apart and representing different population cohorts. Wolfe et al. [3] demonstrated risk of death and likelihood for survival between deceased-donor kidney allograft recipients and wait-listed dialysis patients was equal at 106 and 244 days post-transplant, respectively. Port and colleagues [2] utilized timedependent Cox regression models to compare patient mortality risk between deceased-donor kidney allograft recipients and wait-listed transplant candidates from time of listing. Relative risk of mortality within the first 30 days, days 31-365 and >365 days postkidney transplantation were 2.43, 0.96 and 0.36, respectively. Overall the estimated time from transplantation to equal mortality risk was 117 ± 28 days and to equal cumulative mortality 325 ± 91 days. These analyses confirm the immediate increase in mortality risk posttransplantation but do not shed light on the cause of death within the first year posttransplant.

Previous work has highlighted waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes [15], with absence of waiting time data a limitation of our analysis. Our results demonstrated living-donor kidney transplantation was shown to almost halve

the risk of mortality within the first year, which could be attributed to transplantation in a more timely, planned and expedited fashion (although this is speculative). However, other aspects of our results raise concerns regarding how the waiting list is managed. Firstly, cardiovascular events were the second most common cause of death within the first year and more common in individuals with previous cardiac history. Cardiac disease evaluation of the potential renal transplant recipient is fraught with difficulty, with considerable variability between existing guideline recommendations [16]. Secondly, kidney recipients dying from malignancy as cause of death were more likely to have had a previous cancer history. The evidence for robust cancer screening pretransplantation is limited [17] - however, in the context of previous history, it is imperative that suitable screening and time intervals are adhered to for effective attenuation of post-transplant malignancy risk (although we have no evidence that the higher death rate from malignancy in those with pretransplant cancer history is due to recurrent rather than de novo malignancies).

Current data streams are inadequate in robust reporting of mortality at 1 year post-transplantation. The Transplant Activity Report (2011-2012) published by NHS Blood and Transplant [18] publishes 1-year patient survival data (self-reported by transplant centre) but does not highlight cause of death. Self-reporting also introduces the risk of underreporting due to loss of follow-up. Renal Registry data from the United Kingdom list causes of death in prevalent transplanted recipients but not within the first year post-transplantation. These data are severely compromised due to poor data completeness (less than 50% overall) and have gradually worsened over recent years [19,20]. Therefore, the suboptimal nature of existing registry data output has limited our understanding of death occurring within the first year postkidney transplantation.

A key strength of this study is the unique linking between HES and ONS data streams. The completeness and national coverage of mortality data by ONS, and the ability to perform data linkage analysis, ensure comprehensive data are generated regarding mortality numbers and death certificate registration. The use of the large HES administrative data set ensures generalizability and applicability to the wider transplant community. It also provides the power to detect small effects in meaningful outcomes that are of clinical relevance. Limitations include the absence of unmeasured and/or incompletely measured covariates that are not accounted for in the analysis. It is unlikely that statistics can ever fully adjust for all confounding factors in a cohort study, and this is a limitation inherent to the very nature of observational analyses. The absence of detailed information to contrast both cohorts at baseline is a limitation with the retrospective nature of this cohort study. Finally, the ability for registry data streams to be combined would enhance the robustness of observational cohort studies; for example, linking HES and ONS data sets with both UK Renal Registry and the UK National Transplant database. A richer, comprehensive database allows for a greater ability to discover associations and relationships at the population level for research purposes and overcomes the problem of missing data. There clearly are technical and legal considerations that require resolution [21], but the potential of combining biomedical data remains untapped.

To conclude, death within the first year after kidney transplantation is uncommon in England with an incidence of 3.0%. In certain allograft recipients, the risk of death increases considerably and this risk can be identified pretransplantation. Although quantifying this risk should not absolutely dissuade from proceeding to transplantation per se, it should be utilized to effectively counsel at-risk patients regarding their heightened mortality risk.

Authorship

AS: Designed research study. DF, IB, SK, DR, AS: Performed research study. DF, IB: Collected data. DF, JC, IB, SK, DR, AS: Analysed data. DF, AS: Wrote article. AS: Reviewed article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cause of death in paediatric versus adult kidney allograft recipients in England (2001–2012).

Table S2. Cause of mortality in first year postkidney transplantation comparing early (<3 months) and late (3–12 months).

Table S3. Cause of death among kidney allograft recipients comparing two different transplantation eras – 2001–2006 versus 2006–2012.

References

- Thiruchelvam PT, Willicombe M, Hakim N, Taube D, Papalois V. Renal Transplantation. BMJ 2011; 343: d7300.
- Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of Survival Probabilities for Dialysis Patients vs Cadaveric Renal Transplant Recipients. *JAMA* 1993; 270: 1339.
- 3. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis

- awaiting transplantation and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
- UK Renal Association Clinical Practice Guidelines.
 Assessment of the Potential Kidney Transplant Recipient.
 UK Renal Association, 5th Edition, 2011. www.renal.org/guidelines (last accessed on 14th May 2013).
- European Best Practice Guidelines for Renal Transplantation (part 1). Produced by the EBPG Expert Group on Renal Transplantation. *Nephrol Dial Transplant* 2000; 15 (Suppl 7): 1.
- Djamali A, Samaniego M, Muth B, et al. Medical care of kidney transplant recipients after the first posttransplant year. Clin J Am Soc Nephrol 2006; 1: 623.
- Briggs JD. Causes of death after renal transplantation. Nephrol Dial Transplant 2001; 16: 1545.
- 8. Gill JS, Pereira BJG. Death in the first year after kidney transplantation: implications for patients on the transplant waiting list. *Transplantation* 2003; **75**: 113.
- 9. Grams ME, Massie AB, Schold JD, Chen BP, Segev DL. Trends in the inactive kidney transplant waitlist and implications for candidate survival. *Am J Transplant* 2013; **13**: 1012.
- Hospital Episode Statistics online. www.hesonline.nhs.uk (last accessed on 12th January 2013).
- OPCS-4 Classification NHS Connecting for Health. www. connectingforhealth.nhs.uk (last Accessed on 12th January 2013).
- 12. World Health Organization. International Classification of Diseases (ICD). www.who.int/classifications/icd/en (last accessed on 5th January 2013).
- 13. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453.
- 14. Department for Communities and Local Government. The English Indices of Deprivation 2010. https://www.gov.uk/government/publications/english-indices-of-deprivation-2010 (last accessed on 17th January 2013).
- 15. Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes. *Transplantation* 2002; **74**: 1377.
- Friedman SE, Palac RT, Zlotnick DM, Chobanian MC, Costa SP. A call to action: variability in guidelines for cardiac evaluation before renal transplantation. *Clin J Am* Soc Nephrol 2011; 6: 1185.
- 17. Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: what is the evidence? *Clin J Am Soc Nephrol* 2008; **3**: S87.
- 18. NHS Blood and Transplant. Organ Donation and Transplantation Activity Report 2011/12. http://www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/activity_report_2011_12.pdf (last Accessed 11th February 2013).
- 19. Steenkamp R, Castledine C, Feest T. Chapter 6 Survival and causes of death of UK adult patients on renal replacement

- therapy in 2010: national and centre-specific analyses. *Nephron Clin Pract* 2012; **120**(Suppl. 1): c105.
- 20. Pruthi R, Sinha MD, Casula A, *et al.* Chapter 5 Demography of the UK paediatric renal replacement therapy population in 2010. *Nephron Clin Pract* 2012; **120**(Suppl 1): c93.
- 21. Gliklich RE, Dreyer NA (editors). Chapter 7. Linking Registry Data: Technical and Legal Considerations. Registries for Evaluating Patient Outcomes: A User's Guide. Agency for Healthcare Research and Quality (US), Second Edition. Maryland: Rockville, 2010: 143.