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Kidney transplant outcomes from older deceased donors: A paired kidney analysis by the ERA-EDTA Registry

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Abstract

As the median age of deceased kidney donors rises, updated knowledge of transplant outcomes from older deceased donors in differing donor-recipient age groups is required. Using ERA-EDTA Registry data we determined survival outcomes of kidney allografts donated from the same older deceased donor (55-70 years), and transplanted into one recipient younger and one recipient of similar age to the donor. The recipient pairs were divided into two groups: group 1; younger (median age: 52 years) and older (60 years), and group 2; younger (41 years) and older (60 years). 1,410 adults were transplanted during 2000-2007. Compared to the older recipients the mean number of functioning graft years at 10-years was six months longer in the group 1 and group 2 younger recipients ($p < 0.001$). Ten-year graft survival was 54% and 40% for the group 1 younger and older recipients, and 60% and 49% for the group 2 younger and older recipients. Paired Cox regression analyses showed a lower risk of graft failure (group 1 younger; adjusted relative risk [RRa]:0.57, 95%CI:0.41-0.79, and group 2 younger; RRa:0.63, 95%CI:0.47-0.85) in younger recipients. Outcomes from older deceased donor allografts transplanted into differing donor-recipient age groups are better than previously reported. These allografts remain a valuable transplant resource, particularly for similar-aged recipients.

Introduction

Global variations exist in the criteria for deceased donor kidney allocation (1). Some European deceased donor kidney allocation schemes such as that of the UK, Spain, France and ScandiTransplant take into consideration the age difference between the donor and the potential recipient, whereas others such as EuroTransplant do not (for patients aged <65 years) (1). Deceased donor kidney allocation algorithms that are designed to account for the age difference between the donor and the potential recipient, will where possible allocate younger kidneys to younger patients and older kidneys to older patients (2). However the definition of an acceptable donor-recipient age difference also varies between allocation schemes, for example in Italy a difference between the donor and recipient ages of less than 15 years is preferred, whereas in Spain a difference of less than 10 years is preferred. Whilst allocation schemes may take the donor-recipient age difference into account, older donor kidneys are still being allocated to patients of various ages.

The rationale of age-matching is two-fold; firstly by matching the potential lifespan of the allograft with the recipient, the organ is used efficiently. Secondly, young recipients receiving old deceased donor kidneys have been shown to have worse graft survival outcomes including higher rates of graft failure from rejection compared to young recipients receiving young deceased donor kidneys (3-6). However many of these previous studies were performed in the 1990s and early 2000s when the median age of both the donors and recipients were lower, and graft survival outcomes were worse.

Over the past two decades the demand for transplantable organs has resulted in an increased utilisation of older 'marginal' deceased donor kidneys. Subsequently the median age of deceased kidney donors has steadily increased (7, 8). Within Northern Europe the

median age of deceased kidney donors has risen from approximately 35 years in the 1990s to approximately 55 years in 2015 (9, 10). As the median age of deceased kidney donors and their recipients is now approximately 55 years old, and transplant outcomes over the past two decades have improved (11), updated patient and allograft survival outcomes of kidneys transplanted from deceased donors aged 55 years and over (i.e. above the median deceased donor age) into recipients of differing ages are required.

Using renal registry and transplant registry data from nine European countries/regions, the aim of this study was quantify how long kidney allografts from older deceased donors are expected to function for whilst considering the donor-recipient age difference. Using a paired analysis study design, we analysed patient and allograft survival outcomes of two kidney allografts donated from the *same* deceased donor aged between 55 to 70 years, and transplanted into two recipients of differing ages; a recipient younger than the donor and a recipient of similar age to the donor. This method ensures that a kidney from the same donor is present in both groups, thereby eliminating from the analyses the effects of the donor factors on patient and graft outcomes. Furthermore, we used a novel technique within the kidney transplantation literature, the restricted mean survival time, to quantify the mean difference in the graft survival time between the groups (12).

Materials and Methods

Data collection and study groups

Renal and transplant registries within nine European countries or regions supplying data to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry were asked to identify transplant recipients fulfilling the specified inclusion criteria

(see below). Where necessary additional data required for the survival analyses were obtained from the ERA-EDTA Registry database using a unique anonymised patient identifier (see table 1 for data sources).

The study cohort consisted of all patients aged 18 years and over who received their first kidney only transplant between 2000 and 2007 from a deceased donor aged between 55 to 70 years. As the median deceased donor age in many European countries is 55 years, the age range 55 to 70 was specifically chosen to reflect donors just above the average age of deceased donation. Only cases where *both* kidneys from the *same* deceased donor were transplanted into recipients of differing ages were considered. One transplant recipient had to be within 5 years of the donor's age (as these recipients had a median age at transplantation above the current median transplant age we called these recipients the older recipients), and the second transplant recipient from the same deceased donor had to be at least 6 years or more younger than the donor. Given the large range of the donor-recipient age gradient, that is, the difference in years between the donor and recipient ages, we subdivided the recipient pairs into two groups; termed group 1 and group 2. The cut-off point for the two groups was determined pre-analysis using univariate Cox regression with restricted cubic regression splines analysis (13). The groups were those ≥ 6 to < 13 years younger than the donor and their paired older recipients (group 1) and those ≥ 13 years younger than the donor and their paired older recipients (group 2). The Chi-squared test and Mann-Whitney U test were used to compare the group characteristics.

Statistical analyses

Table 2 provides an overview of the different survival analyses used in this paper, i.e. the survival outcome investigated and analysis method used, the starting point, the event(s) of interest, competing event(s), censoring observations and the potential confounders accounted for in the multivariable analysis. In all of the survival analyses the date of kidney transplantation was taken as the starting point of the analysis, and patients were followed until the event of interest, a censored observation and/or a competing event (see Table 2 for details) or the end of the follow-up period (31st December 2013).

Restricted mean number of functioning graft years

The restricted mean survival is a way in which one quantifies the mean survival of a treatment group measured up to a specific time point. It is computed as the total area under the covariate-adjusted graft survival curve up to a specific time point. By comparing the mean survival of two groups one obtains an assessment of a treatment effect over a time interval (12). This method has the advantages of being relatively easy to understand and can be used even in the presence of non-proportional hazards (14). We estimated the restricted mean survival time of functioning graft years (i.e. the number of years the allograft was functional before loss secondary to graft failure or death with a functioning graft). We repeated this process four times with increasing follow-up times thereby obtaining the mean graft survival time restricted to one, five, seven, and ten years of follow-up (12) (i.e. what was the average time the older donor kidneys were functional for in one, five, seven, and ten years follow-up). We adjusted for important transplant related parameters selected a priori which could influence the functioning of the graft, i.e. cold ischaemia time and human leukocyte antigen (HLA) mismatch (favourable HLA-A, HLA-B and HLA-DR mismatches: 000, 100, 010, 110 versus

all other mismatches). The SAS macro %RESMEAN was used for this analysis (12).

Cumulative risk of graft failure

The cumulative incidence competing risk method was used to estimate the unadjusted 10-year cumulative risk of graft failure and death (15).

Relative risk of allograft failure and patient mortality between younger and older recipients

Cox regression was used to estimate the relative risk of graft failure (defined as graft loss from all causes or death with a functioning graft) (16), and the relative all-cause mortality risk between the older recipient group and the corresponding younger recipient group.

Furthermore, Cox regression analysis was used to estimate the relative risk of graft failure in which the competing event of death was interpreted as a censored event (15) (henceforth termed death-censored graft failure). All Cox regression analyses were stratified by the donor pair, whereby the patient or kidney allograft outcome of the older recipient was directly compared to the patient or kidney allograft outcome of the younger recipient from the same older deceased donor. This removed any donor associated factors from the analysis. Adjustments were made in a step-wise manner. Firstly, we only adjusted for transplant related parameters which could influence graft survival, i.e. cold ischaemia time and HLA mismatch. Secondly, we added recipient factors which could influence graft survival, i.e. recipient sex, primary renal disease and initial modality of renal replacement therapy. A two-tailed p-value of less than 0.05 was considered statistically significant. Analyses were performed using SAS version 9.3 and R version 3.0.2.

Results

Baseline characteristics

In total 1,410 paired kidney transplant recipients from 705 deceased donors aged between 55 to 70 years were included in the study (Table 3). The recipients in group 1 consisted of the younger recipients which were within ≥ 6 to < 13 years of the donor's age (N=336), termed group 1 younger recipients and their corresponding paired older recipients which were within 5 years of the same deceased donor's age (N=336), termed group 1 older recipients, and the recipients in group 2 consisted of the younger recipients which were ≥ 13 years younger than the donor (N=369), termed group 2 younger recipients and their corresponding paired older recipients which were within 5 years of the same donor's age (N=369), termed group 2 older recipients.

Table 3 shows the baseline characteristics of the recipient groups and the corresponding donor details. The median donor-recipient age gradient was 8.1 years (interquartile range [IQR] 7.0 to 10.0) for the group 1 younger recipients, and 20 years (IQR 16.0 to 25.5) for the group 2 younger recipients, whereas both groups of paired older recipients were 0.9 years (IQR -2.0 to 3.0) younger than the donor. The median age at kidney transplantation was 52.0 years (IQR 49.0 to 56.3) for the group 1 younger recipients and 40.7 years (IQR 34.0 to 45.0) for the group 2 younger recipients. The median age of the older recipients in both groups was 60.0 years (IQR 57.0 to 64.0). At the time of donation the deceased donors donating to group 1 had a median age of 61.0 years (IQR 58.0 to 65.0) and the deceased donors donating to group 2 had a median age of 60.0 years (IQR 57.0 to 63.0).

Restricted mean number of functioning graft years

Table 4 shows the restricted mean number of functioning graft years i.e. the number of years the allograft was functional before loss secondary to graft failure or death with a functioning graft. Restricted to 1 year of follow-up there was no difference in the mean number of functioning graft years between the younger and older recipients in group 1 and the younger and older recipients in group 2. The difference in the mean number of functioning graft years between the younger and older recipients in both groups increased with the duration of follow-up. By 10 years follow-up the difference in the mean number of functioning graft years was 0.45 (95% confidence interval [CI]: 0.18 to 0.72, i.e. 5.4 months) and 0.52 (95%CI: 0.27 to 0.77, i.e. 6.2 months longer) years longer in the group 1 younger and group 2 younger recipients respectively compared to their paired older recipients ($p < 0.001$).

Cumulative risk of graft failure

Figure 1 shows the 10-year cumulative risk of graft failure from all causes i.e. graft failure and death with a functioning graft for group 1 (upper panel) and group 2 (lower panel). The 10-year cumulative risk of graft failure from all causes was 46% and 60% for the group 1 younger and older recipients respectively, and 40% and 51% for the group 2 younger and older recipients respectively.

Risk of allograft failure and patient survival

The risk of graft failure (defined as either graft failure or death with a functioning graft) was 43% and 37% lower in the group 1 and group 2 younger recipients respectively relative to their paired older recipients (Table 5). However, there was a similar risk of death-censored graft failure in the group 1 and group 2 younger recipient groups compared to their paired

older recipients (Table 5). This reflected the fact that the risk of patient death was considerably lower in both younger recipient groups (Table 5).

Discussion

In this study we have compared the survival outcomes of kidney allografts from older deceased donors whilst considering the donor-recipient age difference. We examined the outcomes of kidney allografts from the same deceased donor aged between 55 to 70 years (median age of 60 years) transplanted into younger recipients (group 1 with a median of age 52 years or group 2 with a median age of 41 years) with the outcomes when transplanted into an “older” recipient (similar age as donor; median age of 60 years). By performing a paired analysis whereby a donor kidney is present in the younger recipient group and in the corresponding older recipient group, the effects of the donor factors on patient and graft outcomes are essentially eliminated from the analyses. In addition, this study used a method novel in kidney transplantation, whereby graft survival time was derived using the restricted mean survival time. This technique provides easily interpretable and comparable estimates of the number of functioning graft years gained or lost by a treatment over a specified time interval (12, 17). By using the restricted mean survival time method, we found that by 10 years of follow-up the mean number of functioning graft years was six months longer in the younger recipients compared to the corresponding paired older recipients. We found the 10-year graft survival from old deceased donor kidneys to be 54% and 40%, for the group 1 younger and older recipients respectively and 60% and 49% for the group 2 younger and older recipients respectively. This is much higher than the previously reported survival probabilities of 24% at 8 years in recipients aged <55 years of allografts from deceased donors aged ≥55

years (18) and consistent with other studies showing improvements in graft survival within European populations over time (11). In contrast to prior studies we found a similar risk of death-censored graft failure between the younger recipients compared to the older recipients of old deceased donor kidneys.

The 10-year survival probabilities of older deceased donor kidneys reported in this study are higher than the previously quoted survival probabilities (4-6, 18). For example Lim et al., reported that for allografts from donors aged ≥ 55 years, eight year cumulative incidence of death-censored graft failure was 22.3% and 16.4% in recipients aged < 55 years and ≥ 55 years respectively (5). The majority of the previously quoted survival probabilities arise from studies predominantly published in the early 2000s using transplant data from the 1990s (6). Survival probabilities from deceased donors overall (i.e. not stratified by donor age) have improved since the 1990s (11). This probably explains why our survival probabilities from transplants that occurred between 2000 and 2007 are better.

When compared to the current overall European 10-year deceased donor graft survival outcomes, our results are worse. Our 10-year graft survival outcomes from deceased donors aged between 55 to 70 years are approximately 10% lower than the for overall European deceased donor kidney transplant recipients transplanted in the same time period (10-year graft survival probabilities of 71%, 65% and 54%, for a median recipient transplant age of 41, 50 and 60 years respectively -unpublished data from the European Renal Association – European Dialysis and Transplant Association [ERA-EDTA] Registry). There are several physiological changes in the older deceased donor kidney which may explain in part, the lower graft survival probabilities obtained in comparison to the overall graft survival

probabilities for European deceased donor kidney transplant recipients. At the time of transplantation older deceased donor kidneys have been shown to have a reduced number of nephrons (19) and evidence of age-related pathology (20). Furthermore older deceased donor kidneys are not able to mount an adequate repair response following an injury (21). These features also render older deceased donor kidneys more susceptible to the effects of longer cold ischaemia times (22). Although these features in part explain the lower graft survival outcomes we obtained in comparison to the overall graft survival outcomes for European deceased donor kidney transplant recipients, active efforts to reduce cold ischaemia times, in addition to other advances in the procurement of organs and in transplant medicine overall may explain why these results are higher than the historical results. Furthermore, in contrast to prior studies we found a similar risk of death-censored graft failure between younger recipients compared to older recipients of old deceased donor kidneys. The prior studies from the 1990s and 2000s often reported an inferior death-censored graft survival in younger recipients of older donor kidneys (5, 18, 23). As with the improvements in 10-year graft survival these new findings may also be explained by developments in transplant medicine such as organ procurement, transplant preservation and improved immunosuppression medication. Despite the approximately 10% lower survival probability by 10 years follow-up with older donor kidneys, one must remain aware of the benefits of transplantation over dialysis, including improved recipient quality of life and a lower long-term financial burden.

It should be noted that the 10 year transplant outcomes presented in this study are inevitably, a consequence of donations which occurred approximately 10 to 15 years ago. Short term transplant outcomes from older deceased donors have improved in the last few years (6, 24). It is therefore also likely that the 10 year transplant outcomes in a recipient of

an older deceased donor kidney transplanted today will be better than what we present in this paper.

The restricted mean survival time provides an alternative way with which to present time to an event/survival data. One of the benefits of this method is that the result, often expressed in terms of years gained or lost in comparison to an alternative treatment, is easily interpretable for physicians and patients alike. Within the kidney transplant literature we identified one other study using this method to examine kidney allograft survival in older deceased donor kidneys (5). Lim et al., presented mean functioning graft years restricted to 16 years follow-up of 7.1 years for old recipients (≥ 55 years) of old donor kidneys (≥ 55 years) (5). In other words for sixteen years follow-up, the mean functioning graft survival time was 7 years, whereas the mean functioning graft years in our study was between 7 and 7.5 years within a shorter follow-up of 10 years. The cohort used in the study by Lim et al., were transplanted between 1991 and 2006 and therefore the inclusion of transplant outcomes from the 1990s is the likely explanation for the poorer outcomes seen in their study.

This study was not designed to compare survival outcomes of young recipients receiving either young donor kidneys or old donor kidneys. It is well documented that survival outcomes are better for younger recipients if they receive younger donor kidneys (25). Furthermore, younger patients are likely to undergo re-transplantation therefore it is recommended that they should not receive older donor kidneys given the shorter graft survival time and associated risk of sensitization (6). Nevertheless, as shown in this study,

kidney transplantations from older donors into younger recipients do take place, as such, it is important to quantify the survival outcomes of these allografts.

This study is subject to the traditional limitations associated with observational studies, in particular the inability to control for other potential confounding factors. We lacked information on other donor factors which contribute to the risk of graft loss such as donor history of diabetes and cause of death. However, by performing a paired analysis, a kidney from the same older deceased donor was present in the young recipient and the older recipient group. We thereby attempted to eliminate any donor associated factors which may have resulted in bias. However one cannot be completely sure that even though the donor was the same, the kidneys were identical, for example there may have been disparities in kidney size or the presence of cysts between the two kidneys. Although both groups of paired older recipients, i.e. those paired to the younger recipients in group 1 or group 2 had the same median age, there were differences between the groups; of those paired to the group 1 younger recipients (with a median age of 52 years) only 3% had a pre-emptive transplant, compared to 9% of the older recipients paired to the group 2 younger recipients (with a median age of 41). Moreover, the graft survival at 10 years follow-up was lower in the older recipients paired with the group 1 younger recipients compared to the older recipients paired to the group 2 younger recipients (40% versus 49% respectively). This may imply that clinicians selectively allocate the 'better quality' older deceased donor kidneys to the younger recipients and to the healthier older recipients. Therefore the study design employed by this study to overcome the limited donor details available to us, may have introduced a selection bias into the study. As such, these results cannot be considered generalizable to all donor

kidneys from deceased donors aged between 55 to 70 years. We did not have access to transplant factors known to influence allograft outcomes such as the method of graft preservation, panel reactive antibodies and immunosuppression data, or information detailing episodes of delayed graft function or acute rejection therefore we do not know how many episodes each group experienced or the impact of these events. Nor do we have an accurate record of the causes of graft loss. Despite these limitations there are a number of strengths in this study including the paired donor design, the relatively large cohort of recipients from a nine European countries/regions and the reasonably long follow-up time. Furthermore, the novel restricted mean survival time method used in this study provides easily interpretable estimates of the number of years gained or lost or the percentage reduction of expected restricted mean survival time.

Conclusion

The aim of this study was to quantify how long kidney allografts from older deceased donors are expected to function for whilst considering the donor-recipient age difference. In line with kidney transplant outcomes overall, ten year graft survival probabilities from older deceased donors have improved, though they remain approximately 10% lower than the European average kidney transplant survival probabilities. Compared to the older recipients the mean number of functioning graft years at 10 years was six months longer in the younger recipients. Older deceased donor kidneys remain a useful transplant resource, particularly for similar aged recipients.

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Contributors: MP designed the study, prepared the data, wrote the statistical analysis plan, performed the analysis, interpreted the results and drafted and revised the paper. She is the guarantor. KJJ designed the study, co-wrote the statistical analysis plan, interpreted the results and revised the paper; FC interpreted the results and revised the paper; AC contributed data, interpreted the results and revised the paper; HE contributed data, interpreted the results and revised the paper; PF contributed data, interpreted the results and revised the paper; JH contributed data, interpreted the results and revised the paper; GH contributed to the statistical analysis plan, interpreted the results and revised the paper; AH contributed data, interpreted the results and revised the paper; RK contributed data, interpreted the results and revised the paper; ML contributed data, interpreted the results and revised the paper; AM contributed data, interpreted the results and revised the paper; KM contributed data, interpreted the results and revised the paper; JP contributed data, interpreted the results and revised the paper; KGP contributed data, interpreted the results and revised the paper; SSS contributed data, interpreted the results and revised the paper; JPT contributed data, interpreted the results and revised the paper; ZAM interpreted the results and revised the paper; RR designed the study, interpreted the results and revised the paper; VSS designed the study, co-wrote the statistical analysis plan, interpreted the results and revised the paper.

Figure and table legends

Figure 1 Ten-year cumulative risk of graft failure from all causes (i.e. graft failure and death) for the group 1 younger recipients and their paired older recipients (upper panel a & b) and the group 2 younger recipients and their paired older recipients (lower panel c & d).

Table 1 Additional data sources and number of recipients provided by country or region.

Table 2 Overview of the different types of survival analyses used in this paper. The adjustments were made in a step-wise manner; (1) transplant related parameters influencing graft survival, i.e. cold ischaemia time (CIT) and human leukocyte antigen mismatch (HLA MM) and (2) recipient factors influencing graft survival, i.e. recipient sex, primary renal disease and initial modality of renal replacement therapy.

Table 3 Baseline characteristics of the group 1 and group 2 younger recipients and their paired older recipients and the corresponding donor details. (RRT: Renal replacement therapy. HLA: human leukocyte antigen mismatch [favourable HLA-A, HLA-B and HLA-DR mismatches: 000, 100, 010, 110]. IQR: inter-quartile range)

Table 4 Mean number of functioning graft years (95% confidence interval) for the group 1 and group 2 younger and older recipients respectively. Adjusted for cold ischaemia time and human leukocyte antigen mismatch. Differences highlighted in bold indicate a significant difference ($p < 0.05$).

Table 5 Relative risk (RR) of death-censored graft failure, graft failure and patient mortality for the group 1 and group 2 younger recipient groups as compared to their paired older recipients. *Adjusted for cold ischaemia time and human leukocyte antigen (HLA) mismatch. ** Adjusted for cold ischaemia time, HLA mismatch, recipient sex, primary renal disease and initial modality of renal replacement therapy. Differences highlighted in bold indicate a significant difference ($p < 0.05$).

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Table 1 Additional data sources and number of recipients provided by country or region

| Country / Region supplying data | Data source(s) | Number of recipients | Proportion (%) |
|---------------------------------|--|----------------------|----------------|
| Austria | Austrian dialysis and transplant registry | 90 | 6.4 |
| Basque country (Spain) | Information unit about renal patients from the Basque Country | 58 | 4.1 |
| Catalonia (Spain) | Catalan Renal Registry, Catalan Transplant Organization, Health Department, Generalitat of Catalonia | 182 | 12.9 |
| Denmark | Danish Renal Registry and Scandiatransplant | 46 | 3.3 |
| Finland | Finnish Registry for Kidney Diseases and the Finnish Kidney Transplant Registry | 96 | 6.8 |
| the Netherlands | Dutch transplant foundation | 138 | 9.8 |
| Norway | Norwegian Renal Registry | 38 | 2.7 |
| Sweden | Swedish Renal Registry and Scandiatransplant | 96 | 6.8 |
| United Kingdom | United Kingdom Renal Registry and UK Transplant Registry held by NHS Blood and Transplant | 666 | 47.2 |
| Total | | 1410 | 100 |

Table 2 Overview of the different types of survival analyses used in this paper. The adjustments were made in a step-wise manner; (1) transplant related parameters influencing graft survival, i.e. cold ischaemia time (CIT) and human leukocyte antigen mismatch (HLA MM) and (2) recipient factors influencing graft survival, i.e. recipient sex, primary renal disease and initial modality of renal replacement therapy.

| Survival analysis outcome | Survival analysis method | Starting point | Event of interest | Competing event | Censoring observations | Variables adjusted for |
|---|---|---------------------------|--|---------------------------------|--|---|
| Cumulative risk of graft failure | Cumulative incidence competing risk method | Date of kidney transplant | Graft failure | Death with a functioning graft* | End of follow-up period Loss to follow-up | |
| Restricted mean number of functioning graft years | Area under the estimated graft survival function | Date of kidney transplant | Graft failure or Death with a functioning graft | | End of follow-up period or End of 10 year follow-up; whichever event occurred first Loss to follow-up | CIT, HLA MM |
| Relative risk of death-censored graft failure between paired recipients | Pair-stratified Cox regression (cause-specific model) | Date of kidney transplant | Graft failure | | Death with a functioning graft** End of follow-up period Loss to follow-up | 1. CIT & HLA MM. 2. CIT, HLA MM, recipient sex, PRD & first RRT modality |
| Relative risk of graft failure between paired recipients | Pair-stratified Cox regression | Date of kidney transplant | Graft failure or Death with a functioning graft | | End of follow-up period Loss to follow-up | 1. CIT & HLA MM. 2. CIT, HLA MM, recipient sex, PRD & first RRT modality |
| Relative risk of mortality between paired recipients | Pair-stratified Cox regression | Date of kidney transplant | Patient death | | End of follow-up period Loss to follow-up | 1. CIT & HLA MM. 2. CIT, HLA MM, recipient sex, PRD & first RRT modality |
| <p>HLA MM: human leukocyte antigen mismatch. CIT: cold ischaemia time. PRD: primary renal disease. RRT: renal replacement therapy. End of follow-up period: 31st December 2013</p> <p>* Using the cumulative incidence competing risk method, “death with a functioning graft” was interpreted as a competing event.</p> <p>**Using the pair-stratified cause-specific Cox regression, “death with a functioning graft” was interpreted as a censored event (15)</p> | | | | | | |

Table 3 Baseline characteristics of the group 1 and group 2 younger recipients and their paired older recipients and the corresponding donor details. (RRT: Renal replacement therapy. HLA: human leukocyte antigen mismatch [favourable HLA-A, HLA-B and HLA-DR mismatches: 000, 100, 010, 110]. IQR: inter-quartile range)

| | Group 1 | | | Group 2 | | | Missing data (%) all groups |
|--|---|-------------------|---------|---|-------------------|---------|-----------------------------|
| | Younger recipients, (≥6 to <13 years younger) | Older recipients | p-value | Younger recipients, (≥13 years younger) | Older recipients | p-value | |
| Number | 336 | 336 | | 369 | 369 | | |
| Recipient sex (% male) | 63.4 | 64.3 | 0.81 | 63.1 | 68.0 | 0.16 | 0 |
| Age at transplantation, years (median, IQR) | 52.0 (49.0, 56.3) | 60.6 (57.0, 64.0) | <0.01 | 40.7 (34.0, 45.0) | 60.0 (56.7, 63.6) | <0.01 | 0 |
| Pre-transplant dialysis time, years (median, IQR) | 2.1 (1.1, 3.9) | 2.5 (1.3, 4.0) | 0.51 | 2.4 (1.2, 4.2) | 2.5 (1.4, 4.1) | 0.78 | 0 |
| First RRT modality (%); | | | 0.22 | | | 0.29 | 0.1 |
| haemodialysis | 66.4 | 69.1 | | 58.3 | 59.6 | | |
| peritoneal dialysis | 28.0 | 28.0 | | 35.5 | 30.9 | | |
| pre-emptive transplant | 5.7 | 3.0 | | 6.0 | 9.2 | | |
| Primary renal disease (%); | | | 0.25 | | | 0.02 | Unknown |
| diabetes mellitus | 14.3 | 15.5 | | 10.3 | 9.5 | | 16.7% |
| hypertension/renovascular | 9.2 | 10.4 | | 6.8 | 9.2 | | |
| glomerulonephritis/sclerosis | 19.4 | 24.4 | | 27.9 | 19.0 | | |
| Other (including unknown) | 57.1 | 49.7 | | 55.0 | 62.3 | | |
| Donor age, years (median, IQR) | 61.0 (58.0, 65.0) | 61.0 (58.0, 65.0) | NA | 60.0 (57.0, 63.0) | 60.0 (57.0, 63.0) | NA | 0 |
| Donor recipient age gradient, years (median, IQR) | 8.1 (7.0, 10.0) | 0.9 (-2.0, 3.0) | <0.01 | 20.0 (16.0, 25.5) | 0.9 (-2.0, 3.0) | <0.01 | 0 |
| Donor type (%); | | | NA | | | NA | 0 |
| donation after brain death | 89.6 | 89.6 | | 90.5 | 90.5 | | |
| donation after cardiac death | 10.4 | 10.4 | | 9.5 | 9.5 | | |
| Cold ischaemia time, hrs (median, IQR) | 18.4 (15.0, 23.0) | 18.0 (15.2, 21.9) | 0.49 | 20.0 (16.0, 25.5) | 19.0 (15.7, 23.3) | 0.18 | 14.0 |
| HLA mismatch (% favourable HLA-A, -B, -DR mismatches) | 30.1 | 27.4 | 0.44 | 40.1 | 36.3 | 0.29 | 0 |
| Median follow-up time, years (IQR) | 7.9 (5.3, 10.3) | 7.2 (3.7, 9.9) | 0.11 | 7.4 (4.5, 9.6) | 6.9 (3.9, 9.1) | 0.47 | |
| Total follow-up time, years | 2228.20 | 2092.23 | | 2571.47 | 2372.33 | | |

Table 4 Mean number of functioning graft years (95% confidence interval) for the group 1 and group 2 younger and older recipients respectively. Adjusted for cold ischaemia time and human leukocyte antigen mismatch. Differences highlighted in bold indicate a significant difference (p<0.05).

| | Group 1 | | | Group 2 | | |
|-------------------------------|---|--------------------------|--------------------------|---|--------------------------|--------------------------|
| Follow-up time restricted to: | Mean number of functioning graft years for the younger recipients and the paired older recipients | | | Mean number of functioning graft years for the younger recipients and the paired older recipients | | |
| | Younger recipients (95%CI) | Older recipients (95%CI) | Difference (95%CI) | Younger recipients (95%CI) | Older recipients (95%CI) | Difference (95%CI) |
| 1 year | 0.92 (0.89, 0.95) | 0.91 (0.87, 0.95) | 0.02 (-0.03, 0.06) | 0.92 (0.89, 0.95) | 0.92 (0.89, 0.95) | -0.004 (-0.05, 0.04) |
| 5 years | 4.18 (4.08, 4.28) | 4.07 (3.96, 4.17) | 0.12 (-0.03, 0.26) | 4.24 (4.15, 4.33) | 4.09 (3.99, 4.19) | 0.15 (0.01, 0.29) |
| 7 years | 5.58 (5.45, 5.71) | 5.38 (5.24, 5.52) | 0.20 (0.01, 0.39) | 5.70 (5.58, 5.82) | 5.41 (5.23, 5.54) | 0.29 (0.11, 0.47) |
| 10 years | 7.42 (7.24, 7.60) | 6.97 (6.77, 7.17) | 0.45 (0.18, 0.72) | 7.63 (7.47, 7.79) | 7.11 (6.94, 7.29) | 0.52 (0.27, 0.77) |
| | Based on deceased donors with a median age of 61 (interquartile range, 58-65) | | | Based on deceased donors with a median age of 60 (interquartile range, 57-63) | | |

Table 5 Relative risk (RR) of death-censored graft failure, graft failure and patient mortality for the group 1 and group 2 younger recipient groups as compared to their paired older recipients. *Adjusted for cold ischaemia time and human leukocyte antigen (HLA) mismatch. ** Adjusted for cold ischaemia time, HLA mismatch, recipient sex, primary renal disease and initial modality of renal replacement therapy. Differences highlighted in bold indicate a significant difference ($p < 0.05$).

| | Group 1 younger recipients compared to paired older recipients | | | Group 2 younger recipients compared to paired older recipients | | |
|-----------------------------|--|--------------------------|--------------------------|--|--------------------------|--------------------------|
| | unadjusted RR (95%CI) | adjusted RR* (95%CI) | adjusted RR** (95%CI) | unadjusted RR (95%CI) | adjusted RR* (95%CI) | adjusted RR** (95%CI) |
| Death-censored graft | 1.03 (0.71, 1.49) | 0.79 (0.52, 1.19) | 0.84 (0.54, 1.30) | 1.30 (0.95, 1.79) | 1.14 (0.81, 1.62) | 1.04 (0.72, 1.50) |
| Graft failure | 0.69 (0.53, 0.90) | 0.60 (0.45, 0.81) | 0.57 (0.41, 0.79) | 0.79 (0.61, 1.01) | 0.67 (0.50, 0.89) | 0.63 (0.47, 0.85) |
| Patient mortality | 0.49 (0.36, 0.66) | 0.56 (0.43, 0.71) | 0.37 (0.25, 0.54) | 0.23 (0.16, 0.34) | 0.21 (0.14, 0.30) | 0.21 (0.15, 0.31) |