Transplant International

ORIGINAL ARTICLE

# The association of living donor source with patient and graft survival among kidney transplant recipients in the ERA-EDTA Registry – a retrospective study

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## SUMMARY

In this study we aimed to compare patient and graft survival of kidney transplant recipients who received a kidney from a living-related donor (LRD) or living-unrelated donor (LUD). Adult patients in the ERA-EDTA Registry who received their first kidney transplant in 1998–2017 were included. Ten-year patient and graft survival were compared between LRD and LUD transplants using Cox regression analysis. In total, 14 370 patients received a kidney from a living donor. Of those, 9212 (64.1%) grafts were from a LRD, 5063 (35.2%) from a LUD and for 95 (0.7%), the donor type was unknown. Unadjusted five-year risks of death and graft failure (including death as event) were lower for LRD transplants than for LUD grafts: 4.2% (95% confidence interval [CI]: 3.7–4.6) and 10.8% (95% CI: 10.1–11.5) versus 6.5% (95% CI: 5.7–7.4) and 12.2% (95% CI: 11.2–13.3), respectively. However, after adjusting for potential confounders, associations disappeared with hazard ratios of 0.99 (95% CI: 0.87–1.13) for patient survival and 1.03 (95% CI: 0.94–1.14) for graft survival. Unadjusted risk of death-censored graft failure was similar, but after adjustment, it was higher for LUD transplants (1.19; 95% CI: 1.04–1.35). In conclusion, patient and graft survival of LRD and LUD kidney transplant recipients was similar, whereas death-censored graft failure was higher in LUD. These findings confirm the importance of both living kidney donor types.

*Transplant International* 2021; 34: 76–86

**Key words**
donor source, graft survival, kidney transplantation, living donation, patient survival

Received: 11 June 2020; Revision requested: 21 July 2020; Accepted: 28 September 2020;
Published online: 26 October 2020

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doi:10.1111/tri.13759

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## Introduction

The increasing incidence of end-stage kidney disease (ESKD) combined with the inadequate supply of deceased donor kidneys has led to a call for an expansion of the donor pool [1]. Living kidney donation has the potential to increase the donor pool, thereby reducing the waiting time for a kidney transplant [2]. Kidneys from living donors most commonly originate from genetically related individuals (living-related donors, LRD), such as parents, children or siblings. Living donation can also come from a living-unrelated donor (LUD). This may be someone who is emotionally related to the recipient, for example a spouse or a friend, but can also be an unrelated and even unacquainted person, such as a donor via a paired or pooled donation programme or an altruistic donor. Previous studies investigated the effect of the living donor source on patient and graft survival, the majority of which have shown similar patient and graft survival for recipients of kidneys from LUD when compared to LRD [3–9]. By contrast, one study demonstrated better patient survival among recipients of kidneys from LRD compared to those from LUD [10]. However, most previous studies were performed in relatively small patient samples, often from a single centre, and therefore may have lacked the statistical power required to detect relevant differences, or may have represented a selected population.

To the best of our knowledge, there are no large multinational studies available that have investigated the effect of living donor source on the survival of kidney transplant recipients. In this study, we used data from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry to compare patient and graft survival of kidney transplant recipients who received a kidney from a LRD with those transplanted with a graft from a LUD. In addition, we aimed to examine trends over time and to identify differences in causes of death between these two groups.

## Patients and methods

### Study population

For this study, we used data from the ERA-EDTA Registry. It includes data from the 21 national and regional renal registries with complete information on living donor source available: Austria, Dutch and French-speaking Belgium, Bosnia and Herzegovina, Denmark, Finland, France (only if the concerning region was participating in the French REIN registry in the year of the transplantation), Greece, Iceland, Norway, Sweden, Scotland (UK) and the Spanish regions of Andalusia, Aragon, Asturias, Catalonia, Cantabria, Extremadura, Galicia, Madrid and Murcia. These registries provide data on patients receiving kidney replacement therapy (KRT) for ESKD to the ERA-EDTA Registry on an annual basis [11].

We included all adult patients (aged 20 years or older) who received their first kidney transplant from a living donor between 1 January 1998 and 31 December 2017. The transplant recipients were classified into two groups according to donor source: LRD and LUD.

### Data collection and definitions

The core data set of the ERA-EDTA Registry includes the month and year of birth, sex, primary renal disease (PRD), treatment modality at the start of KRT, changes in KRT modality and date and cause of death. There were no missing values for month/year of birth, sex, PRD and treatment modality. Age at kidney transplantation was categorized into four groups: 20–44, 45–64, 65–74 and ≥ 75 years. The PRD was classified according to the coding system of the ERA-EDTA and was

categorized into ten groups: glomerulonephritis/sclerosis, pyelonephritis, polycystic kidneys, adult type, diabetes mellitus type I, diabetes mellitus type II, hypertension, renal vascular disease, miscellaneous and unknown/missing. For survival analysis, the PRD was categorized into four groups: glomerulonephritis, diabetes mellitus, hypertension/ renal vascular disease and other causes. To study the influence of calendar time, the year of kidney transplantation was divided into two time periods, 1998–2007 and 2008–2017. The causes of death were classified using the coding system of the ERA-EDTA and grouped into the following categories: cardiovascular disease (including myocardial ischaemia and infarction, heart failure and cardiac arrest), cerebrovascular accident, infection, cachexia, malignancies, miscellaneous (including suicide) and unknown/unavailable. The ERA-EDTA Registry data set does not include information on donors (e.g. age, comorbidity) or details on transplantations (e.g. human leucocyte antigen (HLA) matching, cold ischaemia time).

### Statistical analysis

The results are expressed as mean and standard deviation (SD) in case of normally distributed data, median and interquartile range (IQR) for non-normally distributed data, or as percentage for categorical data. Comparisons between groups were made using independent t-tests (normally distributed data), Mann–Whitney tests (non-normally distributed data) or chi-squared tests (categorical data).

The distribution of causes of death was analysed for those registries with less than 25% missing or unknown causes of death and the analysis of the causes of death included all countries and regions except France.

LRD and LUD kidney transplantation rates were calculated as the number of transplants performed divided by the general population in millions. Time trends of the transplantation rates were analysed using the Joinpoint regression program [12]. Joinpoint regression is based on Poisson distribution and identifies where a change, a so-called 'joinpoint', in the trend occurs. Changes in the slopes of these trends were calculated as annual percentage change (APC) with a 95% confidence interval (CI) for each segment [13]. For these analyses, only those 14 national and regional registries that had data on donor type available over the entire study period were included: Austria, Dutch- and French-speaking Belgium, Denmark, Finland, Greece, Iceland, Norway, Sweden, Scotland (UK) and the Spanish regions of Andalusia, Asturias, Catalonia and Cantabria.

For all survival analyses, the date of the first kidney transplantation was taken as the starting point, and patients were followed until the event of interest, and censored for loss to follow-up and the end of the study period (31$^{st}$ December 2017) or follow-up period (five or ten years). For patient survival, the event of interest was all-cause death or death due to a specific cause. For graft survival, the event of interest was graft loss (including death with a functioning graft), while for death-censored graft survival the event of interest was graft loss and in this case death was considered a censored observation. Retransplantation after failure of the first graft was not taken into account. We performed Kaplan–Meier and unadjusted and adjusted Cox proportional-hazards analyses. For the latter, the proportional-hazards assumptions were checked using Shoenfeld residuals. Models were adjusted for recipient age at kidney transplantation, sex, PRD, duration of dialysis pre-transplant, country and era of first kidney transplant (all as fixed effects). As a sensitivity analysis, we repeated the aforementioned analyses using a 1:1 matching strategy in which patients were matched based on age and year of transplantation (by 5-year periods).

Because the interaction between living donor type and transplant era was statistically significant for patient survival ($P = 0.04$), the 5-year patient and graft survival was also analysed stratified by the time period of transplantation (1998–2007 versus 2008–2017). In these analyses, only those 14 national and regional registries that had complete data available over the total study period were included.

Finally, because a period on dialysis before kidney transplantation may have influenced the outcomes studied, we repeated all analyses including only those patients who received a pre-emptive transplant (i.e. kidney transplantation before the start of any type of dialysis treatment).

A two-tailed P-value $< 0.05$ was considered statistically significant. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Baseline characteristics

In total, there were 14 370 patients older than 20 years who received a kidney transplant from a living donor between 1998 and 2017. Of the living donor transplants, 9212 (64.5%) were from a LRD and 5063 (35.5%) from a LUD. The remaining 95 patients (0.7%) received a transplant from an unknown living donor source; the

majority was from Catalonia (Spain, $N = 36$, 37.9%) and Aragon (Spain, $N = 28$, 29.5%). These 95 patients were excluded from further analyses.

The characteristics of the kidney transplant recipients are presented in Table 1. At the start of KRT, LRD transplant recipients were younger than LUD transplant

**Table 1.** Kidney transplant recipient characteristics by living donor source in 1998–2017.

| | All patients | KTx from living-related donor | KTx from living-unrelated donor | *P*-value |
|---|---|---|---|---|
| *N*, % | 14 275 (100) | 9212 (64.5) | 5063 (35.5) | |
| Sex, % male | 9355 (65.5) | 5877 (63.8) | 3478 (68.7) | <0.001 |
| Age at onset of KRT in years, median (IQR) | 44.4 (32.9–55.1) | 38.6 (29.2–49.8) | 52.4 (44.5–60.0) | <0.001 |
| Age at onset of KRT, *N* (%) | | | | <0.001 |
| 0–20 years | 159 (1.1) | 151 (1.6) | 8 (0.2) | |
| 20–44 years | 7192 (50.4) | 5866 (63.7) | 1326 (26.2) | |
| 45–64 years | 5947 (41.7) | 2816 (30.6) | 3131 (61.9) | |
| 65–74 years | 924 (6.5) | 360 (3.9) | 564 (11.1) | |
| ≥75 years | 46 (0.3) | 13 (0.1) | 33 (0.7) | |
| Age at first KTx in years, median (IQR) | 45.5 (34.1–56.2) | 39.7 (30.4–51.0) | 53.5 (45.7–61.0) | <0.001 |
| Pre-emptive KTx, *N* (%) | 4602 (32.2) | 2706 (29.4) | 1896 (37.5) | <0.001 |
| Time on dialysis before first KTx (months), median (IQR) | 6.9 (0–17.7) | 7.4 (0–17.8) | 5.7 (0–17.5) | <0.001 |
| PRD (*N*, %) | | | | <0.001 |
| Glomerulonephritis/sclerosis | 4457 (31.2) | 3168 (34.4) | 1289 (25.5) | |
| Pyelonephritis | 1074 (7.5) | 820 (8.9) | 254 (5.0) | |
| Polycystic kidneys adult type | 2028 (14.2) | 928 (10.1) | 1100 (21.7) | |
| Diabetes, type I | 709 (5.0) | 456 (5.0) | 253 (5.0) | |
| Diabetes, type II | 370 (2.6) | 138 (1.5) | 232 (4.6) | |
| Diabetes, type unknown | 137 (1.0) | 70 (0.8) | 67 (1.3) | |
| Hypertension | 989 (6.9) | 584 (6.3) | 405 (8.0) | |
| Renal vascular disease | 135 (1.0) | 71 (0.8) | 64 (1.3) | |
| Miscellaneous | 2565 (18.0) | 1784 (19.4) | 781 (15.4) | |
| Unknown/missing | 1811 (12.7) | 1193 (13.0) | 618 (12.2) | |
| Country (*N*, %) | | | | <0.001 |
| Austria | 845 (5.9) | 464 (5.0) | 381 (7.5) | |
| Bosnia and Herzegovina | 108 (0.8) | 88 (1.0) | 20 (0.4) | |
| Belgium, Dutch-speaking | 251 (1.8) | 185 (2.0) | 66 (1.3) | |
| Belgium, French-speaking | 237 (1.7) | 147 (1.6) | 90 (1.8) | |
| Denmark | 1112 (7.8) | 711 (7.7) | 401 (7.9) | |
| Spain, Andalusia | 432 (3.0) | 251 (2.7) | 181 (3.6) | |
| Spain, Aragon | 52 (0.4) | 49 (0.5) | 3 (0.1) | |
| Spain, Asturias | 39 (0.3) | 36 (0.4) | 3 (0.1) | |
| Spain, Catalonia | 1182 (8.3) | 587 (6.4) | 595 (11.8) | |
| Spain, Cantabria | 19 (0.1) | 14 (0.2) | 5 (0.1) | |
| Spain, Extremadura | 19 (0.1) | 14 (0.2) | 5 (0.1) | |
| Spain, Galicia | 228 (1.6) | 118 (1.3) | 110 (2.2) | |
| Spain, Madrid | 171 (1.2) | 121 (1.3) | 50 (1.0) | |
| Spain, Murcia | 27 (0.2) | 11 (0.1) | 16 (0.3) | |
| Finland | 119 (0.8) | 102 (1.1) | 17 (0.3) | |
| France | 3835 (26.9) | 2423 (26.3) | 1412 (27.9) | |
| Greece | 1267 (8.9) | 1080 (11.7) | 187 (3.7) | |
| Iceland | 99 (0.7) | 71 (0.8) | 28 (0.6) | |
| Norway | 1304 (9.1) | 929 (10.1) | 375 (7.4) | |
| Sweden | 2124 (14.9) | 1215 (13.2) | 909 (18.0) | |
| United Kingdom, Scotland | 805 (5.6) | 596 (6.5) | 209 (4.1) | |

KTx, kidney transplantation; KRT, kidney replacement therapy; SD, standard deviation; IQR, interquartile range; PRD, primary renal disease; Tx, transplantation.

**Table 2.** Risk of mortality and graft failure within 10 years after LRD (*N* = 9212) and LUD (*N* = 5063) kidney transplantation.

| | Number of events | Event rate, % | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* |
|---|---|---|---|---|
| Mortality | | | | |
| Related donor | 613 | 6.7 | 1 | 1 |
| Unrelated donor | 436 | 8.6 | 1.62 (1.43–1.83) | 0.99 (0.87–1.13) |
| Graft failure | | | | |
| Related donor | 1425 | 15.5 | 1 | 1 |
| Unrelated donor | 730 | 14.4 | 1.11 (1.02–1.22) | 1.03 (0.94–1.14) |
| Death-censored graft failure | | | | |
| Related donor | 956 | 10.4 | 1 | 1 |
| Unrelated donor | 402 | 7.9 | 0.90 (0.81–1.02) | 1.19 (1.04–1.35) |

HR, hazard ratio; 95% CI, 95% confidence interval.

*Multivariable model: recipient age at kidney transplantation, sex, primary renal disease, pre-transplant dialysis duration, era of first kidney transplantation and country.

recipients (median [IQR]: 38.6 [29.2–49.8] years versus 52.4 [44.5–60.0] years). The median (IQR) age at transplantation was 39.7 (30.4–51.0) years in LRD transplant recipients versus 53.5 (45.7–61.0) years among LUD transplant recipients. More LUD transplant recipients were males than LRD transplant recipients (68.7% vs. 63.8%).

The percentage of pre-emptive kidney transplants was lower for LRD than for LUD transplant recipients, 29.4% (*N* = 2706) versus 37.5% (*N* = 1896), respectively. Glomerulonephritis/sclerosis was the most common cause of ESKD in both groups (34.4% in LRD and 25.5% in LUD transplant recipients), followed by miscellaneous causes (19.4% and 15.4%, respectively). Polycystic kidney disease, adult type, was a more frequent cause of ESKD in LUD (21.7%) than in LRD transplant recipients (10.1%).

### Trends over time in LRD and LUD kidney transplantation

The 14 national and regional registries that had complete data available over the total study period were included in the analysis to assess the influence of the

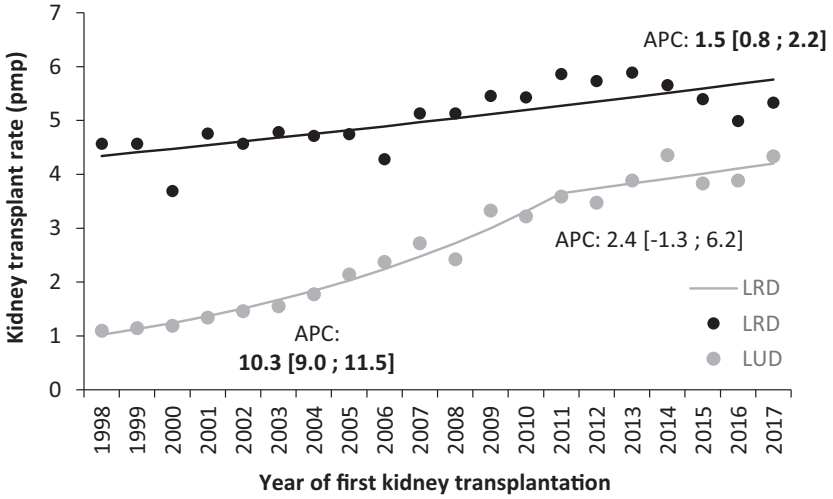



**Figure 1** Kidney transplants from living-related and living-unrelated donors in the period 1998–2017. Annual rates were standardized to the mean age and sex distribution for the whole period. Abbreviations: LRD, living-related donor; LUD, living-unrelated donor; pmp, per million population; APC, annual per cent change. Only those national and regional registries that had complete data available over the total study period from 1998 to 2017 were included: Austria, Dutch- and French-speaking Belgium, Denmark, Finland, Greece, Iceland, Norway, Sweden, Scotland (UK) and the Spanish regions of Andalusia, Asturias, Catalonia and Cantabria.

time period on kidney transplantation (total $N = 9835$; 68.9%). From 1998 to 2017, there was an increase in the rate of both LRD and LUD transplants (Fig. 1). The LRD rate increased steadily with an average of 1.5% per year (APC: 1.5 [0.8; 2.2]). LUD rates increased by 10.5% annually between 1998 and 2011 and seemed to stabilize thereafter (APC: 2.4 [−1.3; 6.2]).

### Patient survival

The analysis of overall patient survival included patients from all registries ($N = 14\ 275$). A total of 1049 patients died within ten years after kidney transplantation, of whom 613 (58.4%) were recipients of kidneys from LRDs and 436 (41.6%) of kidneys from LUDs. In addition, 210 (1.5%) patients were lost to follow-up. The median follow-up time was 6.5 (IQR: 3.1–11.0) years for LRD transplants and 4.7 (IQR: 2.1–8.4) years for LUD transplants.

The unadjusted five- and ten-year patient survival probabilities were higher for LRD transplants (95.8%, 95% confidence interval [CI]: 95.4–96.3 and 88.7%, 95% CI: 87.8–89.6, respectively) than for LUD grafts (93.5%, 95% CI: 92.6–94.3 and 82.0%, 95% CI: 80.1–83.6, respectively). The results of Cox regression analysis comparing the patient survival in the first ten years after LRD and LUD kidney transplantation are presented in Table 2. The unadjusted model showed a 62% higher mortality among LUD transplant recipients when compared with LRD transplant recipients (hazard ratio [HR]: 1.62, 95% CI: 1.43–1.83). However, this association disappeared after adjusting for potential confounders, including recipient age at kidney transplantation, sex, PRD, duration of dialysis pre-transplant, country and era of first kidney transplant (HR: 0.99, 95% CI: 0.87–1.13). Additional analyses showed that it was predominantly the adjustment for age at transplantation that resulted in loss of the association.

The distribution of the causes of death is depicted in Fig. 2. This analysis included all countries and regions except France. Among LRD transplant recipients, cardiovascular disease was the most common cause of death (24.6%), followed by malignancies (21.1%) and infections (20.7%). In recipients of LUD grafts, cardiovascular disease was also the most common cause of death (25.3%), followed by infections (24.3%) and malignancies (21.8%) (absolute numbers are shown in Table 3). The results of the unadjusted cause-specific Cox regression analyses showed that when compared with LRD, LUD transplant recipients had a higher risk of death due to cardiovascular disease (HR: 1.70, 95% CI: 1.30–2.22), infections (HR: 1.91, 95% CI: 1.45–2.53) and malignancies (HR: 1.72, 95% CI: 1.29–2.29) (Table 3); however, these associations disappeared after adjustment for confounders.

Figure 3 presents the unadjusted survival of patients who underwent LRD and LUD kidney transplantation

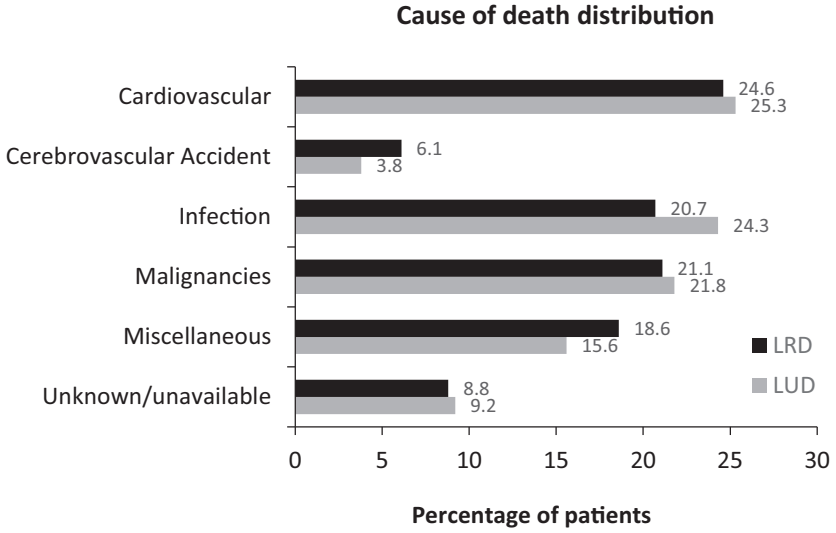



**Figure 2** Causes of death for kidney transplant recipients after living-related and living-unrelated kidney donor transplantation who died within 10 years after transplantation ($n = 892$ recipients). Abbreviations: LRD, living-related donor; LUD, living-unrelated donor. Only those national and regional registries with less than 25% missing or unknown causes of death were included: Austria, Bosnia and Herzegovina, Dutch-speaking Belgium, French-speaking Belgium, Denmark, Finland, Greece, Iceland, Norway, Sweden, Scotland (UK) and the Spanish regions of Andalusia, Aragon, Asturias, Catalonia, Cantabria, Extremadura, Galicia, Madrid and Murcia.

**Table 3.** Risk of mortality according to cause of death within 10 years after LRD ($N$ = 6789) and LUD ($N$ = 3651) kidney transplantation.

| | Number of events | Event rate, % | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* |
|---|---|---|---|---|
| Cardiovascular disease | | | | |
| Related donor | 128 | 1.9 | 1.0 | 1.0 |
| Unrelated donor | 94 | 2.6 | 1.70 (1.30–2.22) | 1.02 (0.77–1.36) |
| Cerebrovascular accident | | | | |
| Related donor | 32 | 0.5 | 1 | 1 |
| Unrelated donor | 14 | 0.4 | 1.00 (0.53–1.88) | 0.74 (0.38–1.46) |
| Infections | | | | |
| Related donor | 108 | 1.6 | 1 | 1 |
| Unrelated donor | 90 | 2.5 | 1.91 (1.45–2.53) | 1.19 (0.88–1.61) |
| Malignancies | | | | |
| Related donor | 110 | 1.6 | 1 | 1 |
| Unrelated donor | 81 | 2.2 | 1.72 (1.29–2.29) | 0.99 (0.73–1.35) |
| Miscellaneous | | | | |
| Related donor | 97 | 1.4 | 1 | 1 |
| Unrelated donor | 58 | 1.6 | 1.38 (0.99–1.91) | 0.90 (0.63–1.28) |
| Unknown/unavailable | | | | |
| Related donor | 46 | 0.7 | 1 | 1 |
| Unrelated donor | 34 | 0.9 | 1.68 (1.08–2.62) | 1.31 (0.79–2.17) |

Only those national and regional registries with less than 25% missing or unknown causes of death were included: Austria, Bosnia and Herzegovina, Dutch-speaking Belgium, French-speaking Belgium, Denmark, Finland, Greece, Iceland, Norway, Sweden, Scotland (UK) and the Spanish regions of Andalusia, Aragon, Asturias, Catalonia, Cantabria, Extremadura, Galicia, Madrid and Murcia.

HR, hazard ratio; 95% CI, 95% confidence interval.

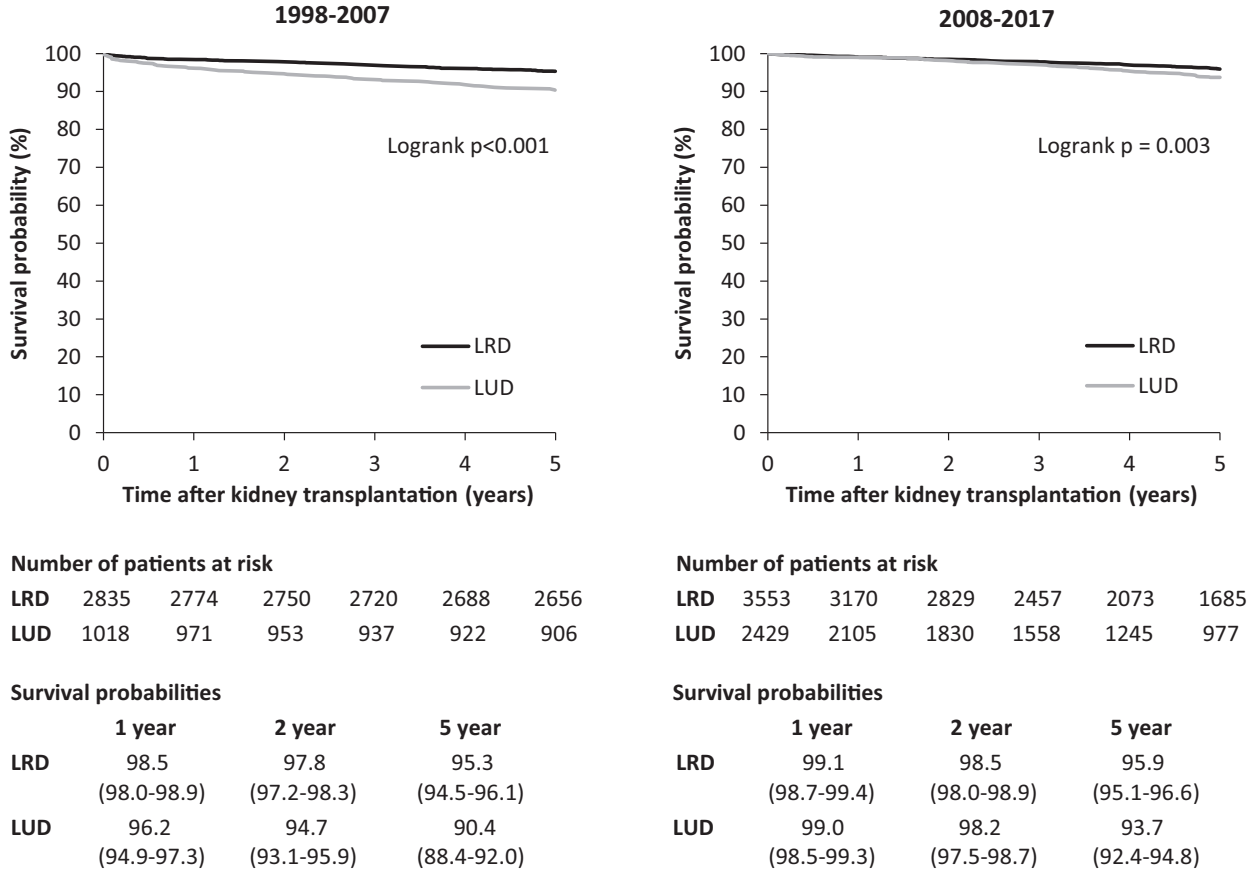
*Multivariable model: recipient age at kidney transplantation, sex, primary renal disease, pre-transplant dialysis duration, era of first kidney transplantation and country.

in 1998–2007 and 2008–2017. Only the 14 registries with data available over the entire study period were included in this analysis (total $N$ = 9835; 68.9%). Between 1998 and 2007, unadjusted patient survival was higher in the LRD transplant recipients than in the LUD transplant recipients, with 5-year survival probabilities of 95.3% (95% CI: 94.5–96.1) and 90.4% (95% CI: 88.4–92.0), respectively. Also in the period 2008–2017, the 5-year patient survival probability was higher in the LRD transplant recipients (95.9%, 95% CI: 95.1–96.6) than in the LUD transplant recipients (93.7%, 95% CI: 92.4–94.8). In both LRD and in LUD transplant recipients, the risk of death was lower in the most recent time period. The results of the adjusted Cox regression analyses by era showed no difference in the risk of death between LUD and LRD transplant recipients in 2008–2017 when compared to 1998–2007 (Table 4).

## Graft survival

The analysis of graft survival included patients from all registries ($N$ = 14 275). Kidney graft failure (including death as event) occurred in 2155 patients, of whom 1425 (66.1%) were LRD graft recipients and 730 (33.9%) LUD graft recipients. The unadjusted five- and ten-year graft survival probabilities were higher after LRD (89.2%, 95% CI: 88.5–89.9 and 75.0%, 95% CI: 73.7–76.2, respectively) than after LUD kidney transplantation (87.8%, 95% CI: 86.7–88.8 and 72.6%, 95% CI: 70.6–74.6, respectively), and the unadjusted Cox regression model showed an 11% increase in graft failure among LUD graft recipients when compared to LRD graft recipients (HR: 1.11, 95% CI: 1.02–1.22; Table 2). Again, this association disappeared after adjusting for the potential confounders, recipient age at transplantation, sex, PRD, duration of dialysis pre-transplant, country and era of first kidney transplant (HR: 1.03, 95% CI: 0.94–1.14). Similar to the analyses of patient survival, the adjustment for age was the principal confounding factor that removed the effect of donor source on graft survival.

There were 956 LRD and 402 LUD transplant recipients who remained alive after their graft failed. The unadjusted analysis of death-censored graft failure




**Number of patients at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| **LRD** | 2835 | 2774 | 2750 | 2720 | 2688 | 2656 |
| **LUD** | 1018 | 971 | 953 | 937 | 922 | 906 |

**Number of patients at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| **LRD** | 3553 | 3170 | 2829 | 2457 | 2073 | 1685 |
| **LUD** | 2429 | 2105 | 1830 | 1558 | 1245 | 977 |

**Survival probabilities**

| | 1 year | 2 year | 5 year |
|---|---|---|---|
| **LRD** | 98.5 (98.0-98.9) | 97.8 (97.2-98.3) | 95.3 (94.5-96.1) |
| **LUD** | 96.2 (94.9-97.3) | 94.7 (93.1-95.9) | 90.4 (88.4-92.0) |

**Survival probabilities**

| | 1 year | 2 year | 5 year |
|---|---|---|---|
| **LRD** | 99.1 (98.7-99.4) | 98.5 (98.0-98.9) | 95.9 (95.1-96.6) |
| **LUD** | 99.0 (98.5-99.3) | 98.2 (97.5-98.7) | 93.7 (92.4-94.8) |

**Figure 3** Unadjusted 5-year patient survival probabilities for living-related donor (LRD) and living-unrelated donor (LUD) kidney transplants by transplant era, in 1998–2007 and 2008–2017.

**Table 4.** Risk of mortality and of graft failure within 5 years after LRD and LUD kidney transplantation, by transplant era (1998–2007 (LRD, *N* = 2835; LUD, *N* = 1018) and 2008–2017 (LRD, *N* = 3553; LUD, *N* = 2429).

| | 1998–2007 | | | | 2008–2017 | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* events | Event rate | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* | *N* events | Event rate | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* |
| Mortality | | | | | | | | |
| Related donor | 131 | 4.6% | 1 | 1 | 106 | 3.0% | 1 | 1 |
| Unrelated donor | 97 | 9.5% | 2.13 (1.64–2.76) | 1.32 (0.99–1.76) | 102 | 4.2% | 1.52 (1.15–1.99) | 0.88 (0.66–1.18) |
| Graft failure | | | | | | | | |
| Related | 348 | 12.3% | 1 | 1 | 271 | 7.6% | 1 | 1 |
| Unrelated donor | 153 | 15.0% | 1.25 (1.03–1.51) | 1.19 (0.96–1.46) | 204 | 8.4% | 1.17 (0.98–1.40) | 1.03 (0.84–1.26) |
| Death-censored graft failure | | | | | | | | |
| Related | 242 | 8.5% | 1 | 1 | 180 | 6.8% | 1 | 1 |
| Unrelated donor | 75 | 7.4% | 0.88 (0.68–1.14) | 1.16 (0.87–1.55) | 123 | 5.1% | 1.06 (0.84–1.33) | 1.29 (1.00–1.68) |

Only those national and regional registries that had complete data available over the total study period from 1998 to 2017 were included: Austria, Dutch- and French-speaking Belgium, Denmark, Finland, Greece, Iceland, Norway, Sweden, Scotland (UK) and the Spanish regions of Andalusia, Asturias, Catalonia and Cantabria.

HR, hazard ratio; 95% CI, 95% confidence interval.

*Multivariable model: recipient age at kidney transplantation, sex, primary renal disease, pre-transplant dialysis duration and country.

showed no association between donor source and graft failure (HR 0.90, 95% CI: 0.81–1.02), whereas the risk of death-censored graft failure was higher in LUD than in LRD transplant recipients (HR 1.19, 95% CI: 1.04–1.35) after adjustment for confounders (Table 2).

When stratified by time period, the graft failure risk was similar for LRD and LUD transplant recipients after adjustment (Table 4). However, the increased risk of death-censored graft failure for LUD transplant recipients was only statistically significant for the cohort in 2008–2017.

In the sensitivity analysis based on an age-matched cohort ($N = 8432$), we found that both patient and graft survival results were very similar to the findings of the main analysis (Table S1).

Repeating the analyses only for those patients who received a pre-emptive kidney transplant ($N = 4602$; 32.2%) resulted in similar adjusted HRs for patient, graft and death-censored graft survival (0.94, 95% CI: 0.69–1.28; 1.15, 95% CI: 0.93–1.42; and 1.36, 95% CI: 1.04–1.79, respectively) compared with the analyses using the entire dataset.

## Discussion

This is the largest study on the effect of the living donor source on the survival of patients undergoing kidney transplantation reported to date. Using data from 21 European renal registries from 12 countries, we demonstrate that kidney donation from both LRD and LUD has increased over time. In addition, we found that patient and graft survival (including death as event) were similar among recipients of LRD and LUD kidneys, while death-censored graft survival was higher for LRD transplants between 2008 and 2017. In both groups, there was a trend towards improved patient and graft survival over time.

Most previous studies that investigated the effect of the living donor source on patient survival have demonstrated a similar patient survival for recipients of LRD versus LUD kidneys. Short-term (1–3 years) patient survival rates were comparable for LRD and LUDs grafts in studies carried out in the United Kingdom, Italy, Egypt and the United States [3,6,7,9]. An Iranian study on long-term patient survival after LRD and LUD kidney transplantation reported similar 10-year, 20-year and 25-year survival probabilities [4,5]. By contrast, a study in the United States showed that 10-year patient survival among recipients of LUD transplants was worse than that of LRD transplants (86% versus 63%, respectively) [10]. This study was, however, carried out over 20 years ago and immunosuppressive therapies have improved considerably since then.

In addition to patient survival, graft survival after kidney transplantation is also of considerable interest to potential donors, candidate recipients, health professionals and payers. Consistent with our findings, the majority of previous studies found that graft survival was similar for LRD and LUD graft recipients. Despite the higher numbers of HLA mismatches among recipients of LUD kidneys, rejection rates were comparable in both groups. This can likely be attributed to potent immunosuppressive regimens [14].

Graft survival rates vary among kidney transplant recipients due to several factors, including recipient and donor characteristics, surgical techniques, delayed graft function, presence of donor-specific HLA antibodies, immunosuppressive regimens and acute rejection rates [15,16]. The donor source plays a crucial role in graft survival. Living donor kidneys are associated with better graft survival when compared to deceased donor kidneys, mostly due to the better quality of the grafts (i.e. less ischaemic injury), short ischaemia time, scheduled surgery and higher probability of pre-emptive transplantation [17–19].

While previous studies generally used overall graft failure (including death as an event) as the primary outcome, we also analysed whether the donor source was associated with death-censored graft failure. Remarkably, we found that after adjustments, the risk of death-censored graft failure was higher in LUD than in LRD transplant recipients, whereas the overall risk of graft failure was similar in both groups. We cannot explain this discrepancy, but we speculate that it might be explained by the fact that the higher risk of graft failure without death (HR of 1.19) and the similar risk of death for LUD transplant recipients (HR of 0.99) average out to the hazard ratio of 1.03 (95% CI: 0.94–1.14) for overall graft failure (including death). We can also speculate that our finding of a higher rate of graft failure among LUD transplants might be due to the older age and the greater proportion of patients with diabetes mellitus type II and hypertension (as the PRD) among the LUD transplant recipients. Nevertheless, our study showed high unadjusted ten-year graft survival rates for both LRD and LUD transplant recipients (75% and 73%, respectively).

Our findings are important for healthcare professionals and policy makers when considering kidney transplantation from living donors as a treatment modality for KRT. This notion may lead to improvements in health policies concerning kidney donations from non-

relatives, making the procedure acceptable in countries where it is considered illegal. In addition, awareness about the possibility of altruistic donation could be increased in the general population. Our results are also important for patients, so that they can discuss potential donation with genetically non-related acquaintances leading to more people coming forward as potential living donors.

Because both short-term and long-term patient and graft survival rates were found to be similar for LRD and LUD transplants, health policies should be advocated for promoting living donation and recruiting more unrelated organ donors.

In our study, we found that 32.2% of living donor kidney transplants were pre-emptive transplants. Interestingly, the percentage of pre-emptive transplants was lower for LRD than for LUD graft recipients. Efforts to promote living kidney donation should also aim at increasing the number of pre-emptive transplants to further improve recipient and graft survival.

The most important strength of our study lies in the very large sample size and relatively long follow-up time. Data from 21 national and regional renal registries in 12 European countries are included, covering a total population of 176 million individuals over a 20-year time period [20], with no missing data except from the cause of death (34%). Our study is, however, limited by the lack of important information on the recipients, such as comorbid conditions and transplant-related factors, including HLA matching, immunosuppressive regimens and acute rejection episodes, all of which influence kidney transplant outcomes. Moreover, information on the donors, including their age, was unavailable, which made it impossible to adjust for these factors. We believe that most donor and transplant recipient factors are not very different for LUD versus LRD transplants. However, there may be a difference in donor age since younger patients not infrequently receive a donor kidney from an older LRD, while this occurs less often with LUD transplants. It is conceivable that higher donor age could have a negative impact on patient and graft survival among LRD kidney recipients when compared with recipients of LUD grafts [21,22]. In addition, these findings may not be generalizable to other countries where transplant practice may vary.

In conclusion, the frequency of kidney transplantation from living donors increased over the past 20 years. We showed a comparable patient and graft survival for both LRD and LUD kidney transplants, with improvements of both occurring over time, particularly in the most recent years. Only the risk of death-censored graft loss was higher for LUD transplant recipients than LRD transplant recipients. Our findings highlight the importance of increasing awareness of living kidney donation, especially from unrelated donors.

## Authorship

SAE, MN, AK and KJJ: were responsible for the study design, statistical analysis and interpretation of the data. SB, ES, JMAD, TL, AVR, JK, CSP, FO, FC, RP, MA, JGH and ZAM: represent the national and regional renal registries that participated in the study. They collected the data and were involved in the interpretation of the results for their own country or region. SAE: drafted the manuscript with input from all other authors. All authors have critically reviewed the manuscript version to be published and gave their final approval.

## Funding

The ERA-EDTA Registry is funded by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA).

## Conflict of interest

The authors have declared no conflicts of interest.

## Acknowledgements

We would like to thank the patients and the staff of the dialysis and transplant units for contributing the data via their national and regional renal registries. Furthermore, we gratefully acknowledge the following registries and persons for their contribution of the data: Austrian Dialysis and Transplant Registry [OEDTR] (R. Kramar); Dutch-speaking Belgian Society of Nephrology [NBVN] (M. Couttenye, F. Schroven and J. De Meester); French-speaking Belgian Society of Nephrology [GNFB] (JM. des Grottes); Renal Registry Bosnia and Herzegovina (H. Resić, B Jakovljevic and M Tomić); Danish Nephrology Registry [DNS]; Finnish Registry for Kidney Diseases (P. Finne, J. Helve and P.H. Groop); France: The Epidemiology and Information Network in Nephrology [REIN] (M. Lassalle and C. Couchoud); Hellenic Renal Registry (G. Moustakas); Icelandic End-Stage Renal Disease Registry; Norwegian Renal Registry (A. Åsberg); Swedish Renal Registry [SRR] (M. Stendahl, H. Rydell, M. Evans, K.G. Prütz, T. Lundgren and M. Segelmark); Scottish Renal Registry [SRR] (All of the Scottish renal units); and the regional registries of

Andalusia [SICATA] (P. Castro de la Nuez (on behalf of all users of SICATA)), Aragon (F. Arribas Monzón and J.I. Sanchez Miret), Asturias (P. Beltrán, J.R. Quirós, and RERCA Working Group), Cantabria (J.C. Ruiz San Millán, O. Garcia Ruiz, and C. Piñera Haces), Catalonia [RMRC] (E. Arcos, J. Comas, and J. Tort), Community of Madrid (M.I. Aparicio de Madre), Extremadura (All the renal units (Nephrology and Dialysis)), Galicia (E. Bouzas-Caamaño), Renal Registry of the Region of Murcia (I. Marín Sánchez); and the other ERA-EDTA Registry committee members not mentioned above for their advice in the analysis and the drafting of this paper: C. Zoccali, P. Ambühl, M. Evans, P. Finne, J. Harambat, L. Mercadal, M. Nordio, S.S. Sørensen and E. Vidal; and R. Boenink in the Registry office for data collection and management.

The ERA-EDTA Registry is funded by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). This article was written by S. Abd ElHafeez, M. Noordzij, A. Kramer, S. Bell, E. Savoye, J.M. Abad Diez, T. Lundgren, A.V. Reisæter, J. Kerschbaum, C. Santiuste de Pablos, F. Ortiz, F. Collart, R. Palsson, M. Arici, J.G. Heaf, Z.A. Massy and K.J. Jager on behalf of the ERA-EDTA Registry which is an official body of the ERA-EDTA (European Renal Association – European Dialysis and Transplant Association).

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** Risk of mortality and graft failure within 10 years after LRD (N=4216) and LUD (N=4216) kidney transplantation in the matched cohort

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