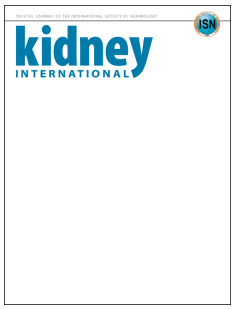
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Results in the ESPN/ERA-EDTA Registry suggest disparities in access to kidney transplantation but little variation in graft survival of children across Europe.

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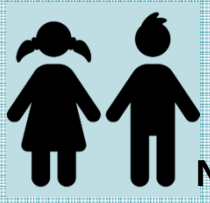
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Results in the ESPN/ERA-EDTA Registry suggest disparities in access to kidney transplantation but little variation in graft survival of children across Europe.

Cohort

ESPN/ERA-EDTA Registry



N=6909

- 37 European countries
- Age < 20 years
- RRT initiation:2007-2015
- GDP tertiles

european society for paediatric nephrology

era edta LEADING EUROPEAN NEPHROLOGY

Five year

	Tx rate	Graft survival
Low-income	48.8%	87.3%
Middle-income	76.3%	87.3%
High-income	92.3%	88.8%



GDP alone explained **66%** of the international variation in transplantation rates.

CONCLUSION:

Despite large disparities in access to transplantation across Europe, graft failure rates were relatively similar.

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Bonthuis et al, 2020

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[QUERY TO AUTHOR: title and abstract rewritten by Editorial Office – not subject to change]

Results in the ESPN/ERA-EDTA Registry suggest disparities in access to kidney transplantation but little variation in graft survival of children across Europe.

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Abstract

One of the main objectives of the European health policy framework is to ensure equitable access to high-quality health services across Europe. Here we examined country-specific kidney transplantation and graft failure rates in children and explore their country- and patient-level determinants. Patients under 20 years of age initiating kidney replacement therapy from January 2007 through December 2015 in 37 European countries participating in the ESPN/ERA-EDTA Registry were included in the analyses. Countries were categorized as low-, middle-, and high-income based on gross domestic product. At five-years of follow-up, 4326 of 6909 children on kidney replacement therapy received their first kidney transplant. Overall median time from kidney replacement therapy start to first kidney transplantation was 1.4 (inter quartile range 0.3-4.3) years. The five-year kidney transplantation probability was 48.8% (95% confidence interval: 45.9-51.7%) in low-income, 76.3% (72.8-79.5%) in middle-income and 92.3% (91.0-93.4%) in high-income countries and was strongly associated with macro-economic factors. Gross domestic product alone explained 66% of the international variation in transplantation rates. Compared with high-income countries, kidney transplantation was 76% less likely to be performed in low-income and 58% less likely in middle-income countries. Overall five-year graft survival in Europe was 88% and showed little variation across countries. Thus, despite large disparities transplantation access across Europe, graft failure rates were relatively similar. Hence, graft survival in low-risk transplant recipients from lower-income countries seems as good as graft survival among all (low, medium, and high risk) graft recipients from high-income countries.

Keywords: end-stage renal disease, kidney transplantation, pediatric nephrology, disparities, kidney graft survival.

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Introduction

Kidney transplantation is the optimal treatment for children with end-stage kidney disease (ESKD).[1] Compared with dialysis, kidney transplantation is associated with better patient survival, psychosocial development, quality of life, and imposes fewer restrictions on everyday life.[2] Consequently, it is vital to aim for pre-emptive kidney transplantation or to reduce the period on dialysis by transplanting these children as soon as possible, and to optimize graft survival.[3-5]

One of the main focus points of the European health policy framework is to ensure equitable access to high-quality health services across Europe.[6] However, we previously established inequalities in access to pediatric renal replacement therapy (RRT) throughout Europe,[4,7] as well as substantial variation in mortality rates of patients on RRT between countries.[8] Most of these disparities were explained by differences in country macroeconomics, which limited the quality of- and access to treatment, particularly in the youngest patients.[7] The risk of death in transplanted children is exceptionally low, and the recipients are more likely to experience graft failure.[9]

Considering the diversity of kidney transplantation policies and practices across Europe, access to pediatric kidney transplantation and graft failure rates are likely to vary between countries.[4,10,11] Although international differences in kidney transplantation- and graft failure rates have been described in the adult kidney transplant population in high-income countries,[12] the existence of any country-level differences remains largely unknown in the pediatric population. In this study, we aim to determine the extent of country variation in kidney transplantation- and graft failure rates, and to assess the impact of both patient- and country-level determinants in explaining this variation.

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Results

Patient characteristics

Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT) were the most common primary renal disease (PRD) (33.5%) in 6,909 children from 37 European countries who started RRT between 2007 and 2015 (Table 1). Most patients initiated RRT on hemodialysis (HD) (43.6%), whereas 19.2% received a pre-emptive kidney transplant. Compared with patients treated in low- and middle-income countries, high-income countries had a higher percentage of boys on RRT, had a different PRD distribution, performed a higher percentage of pre-emptive and living-related donor kidney transplantations, and patients were younger at the time of transplantation.

Access to kidney transplantation

During 5-year since RRT initiation, 4326 patients from 35 countries received a first kidney transplant after a median of 1.4 (Interquartile range (IQR): 0.3-4.3) years on dialysis. The 5-year cumulative kidney transplant incidence was 77.4% (95% CI: 76.0-78.6%); 6.5% (95% CI: 5.8-7.3%) had died before receiving a transplant (Figure 1).

Access to kidney transplantation differed considerably by country income. The 5-year cumulative transplant incidence was 48.8% (95% CI: 45.9-51.7%) in low-income countries, 76.3% (95% CI: 72.8-79.5%) in middle-income countries, and 92.3% (95% CI: 91.0-93.4%) in high-income countries (P<0.001; Figure 1). Similarly, the median time to transplantation was 5.3 (IQR: 1.0-P75 not reached) years in low-income, 2.0 (IQR: 0.8-4.7) years in middle-income, and 0.8 (IQR: 0.0-2.0) years in high-income countries. Mortality on dialysis prior to kidney transplantation was highest in low-income countries (10.4%, 95% CI: 8.8-12.2%), followed by middle-income (6.9%, 95% CI: 5.2-8.8%), and was lowest in high-income countries (3.1%, 95% CI: 2.5-3.8%). In all three income groups, the majority of grafts were donated by deceased donors.

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The average 5-year kidney transplantation rate in Europe was 477.2 per 1000 patient years at risk (95% CI: 467.1 to 487.6), with large differences between countries, ranging from 76.5 (95% CI: 0.0 to 163.0) in Bosnia and Herzegovina to 1796.6 (95% CI: 1384.4 to 2208.8) per 1000 patient years in Norway (Figure 2). The kidney transplantation rate in most low-income countries (Russia, Turkey, Romania, Ukraine, Bulgaria, Bosnia and Herzegovina, Republic of North Macedonia) was at least 3 SD lower than the European average. This was also the case for three middle-income countries (Greece, Slovakia, and Croatia). By contrast, the majority of high-income countries (UK, France, Spain, the Netherlands, Sweden, Austria, Finland, Denmark, Switzerland, and Norway) had kidney transplantation rates of at least 3 SD higher than the European average. The kidney transplantation rates for other countries did not differ from the European average beyond what could be explained by random variation alone.

Determinants of access to kidney transplantation

National wealth was strongly associated with the likelihood of receiving a kidney transplant and accounted for 66.6% of the variation between countries. Compared with patients in high-income countries, patients in low-income countries were 65% (hazard ratio [HR] 0.35, 95% CI: 0.26-0.48) less likely to receive a kidney transplant (P<0.001; Table 2). Health expenditure was also associated with access to transplantation (HR 1.19 per 1000 USD increase, 95% CI: 1.12-1.26), and accounted for 58.5% the variation between countries. The variation between countries in access to transplantation increased by 14.5% after adjustment for patient age. In other words, the existing differences between countries regarding access to transplantation *widened* after adjusting for patient age. This indicates that country differences in the age distribution of transplant recipients may be concealing the true variation in kidney transplant rates across Europe (Figure S1). Other patient factors affected the variation in access to kidney transplantation between countries only to a lesser extent.

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We identified an interaction between patient age at RRT and country income group. In high-income countries, the youngest patients had the lowest access to transplantation, whereas this was not the case in low income countries; patients below 2 years of age when commencing RRT had a non-significantly different likelihood of receiving a transplant at 5 years compared with patients older than 13 years of age (aHR: 1.14, 95% CI: 0.90-1.45).

We also identified an interaction between the percentage of living donors and country income group. In low income countries, a percentage of less than 29.8% living donors was associated with a higher likelihood to receiving a transplant (HR: 1.97, 95% CI: 1.02-3.80), whereas in middle income countries, a percentage of less than 57.7% living kidneys was associated with a lower likelihood of receiving a kidney transplant. We found no association between the percentage of living donors and access to kidney transplantation in high income countries.

Kidney graft failure

The overall 5-year graft survival in Europe was 88.3% (Figure 3), and the 5-year graft failure rate was 31.3 per 1000 patient-years at risk. The crude 5-year graft failure rates per country are shown in Figure 4. The country-specific rates ranged from 0 to 132.0 graft failures per 1000 patient-years. Crude graft failure rates were more than 2 SD lower than the European average in Portugal, and more than 2 SD higher for Spain, Greece, Lithuania, and Croatia. The graft failure rates for other countries did not differ from the European average other from what could be explained by random variation alone.

Determinants of kidney graft failure

The 5-year risk of graft failure did not differ by income group (Table 3), nor by health expenditure. Patients who received a pre-emptive kidney transplant had a lower risk of graft failure compared with patients who started RRT on dialysis (aHR: 0.63, 95% CI: 0.49-0.81). Similarly, patients who

received a kidney from a living donor had a lower graft failure risk than those who received a deceased donor graft (aHR: 0.57, 95% CI: 0.45-0.73). Very young patients (<2 years at transplantation) had a higher risk of graft failure (aHR: 1.71, 95% CI: 1.06-2.75) compared with those >13 years. The variation in graft failure rates between countries increased after adjustment for income group (Proportional change in variance (PCV) increased by 21.1%), donor type (PCV: +18.4%), age at transplantation (PCV:+7.4%), and health expenditure (PCV: +2.7%) (Figure S2). Timing of kidney transplantation (PCV: -6.5%) and PRD group (PCV: -7.9%) explained the country variation in graft failure only to a marginal extent, while adjustment for sex had no effect on country variation.

Sensitivity analyses

In sensitivity analyses we explored the effect of income inequality estimated by the GINI coefficient on access to transplantation, as well as on the risk of graft failure across countries. The GINI coefficient accounted for 9.0% of the variation in access to transplantation across countries. The likelihood of receiving a transplant did not differ for countries with a GINI index below 34.7%. However, patients treated in countries with a GINI index ≥ 34.7% had a significantly lower access to transplantation at 5 years compared to patients treated in countries with the lowest GINI index (≤28.5%) (Table S1a). The percentage of GDP spent on health care accounted for 24.9% of the variation in kidney transplantation rates across countries, and countries with a smaller portion of their GDP spent on health care had a significantly lower likelihood of transplantation compared with countries spending more of their budget on health care. None of these factors were associated with 5-year graft failure risk (Table S1b).

As a proxy for best-practice, we compared the transplant rate of individual countries with a benchmark derived from the average transplant rate in high income countries. With the exception of Estonia, the kidney transplantation rate in every low-and middle-income country was at least 3 SD lower than this benchmark. Interestingly, also the transplantation rates in the high-income countries

Belgium and United Kingdom were at least 3 SD below this benchmark, whereas the transplant rates in Spain, the Netherlands, Denmark and Norway were 3 SD higher than this benchmark (Figure S3). Similarly, we compared country graft failure rates with a benchmark derived from the average graft failure rate in high-income countries (Figure S4). Graft failure rates in Russia and Slovakia were now significantly higher compared with this benchmark.

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Discussion

The European Union aims to achieve equity in access to high-quality health care across all member states.[6] Nonetheless, here we demonstrate country differences in access to pediatric kidney transplantation across Europe, with lower access to transplantation found in lower-income countries. Fortunately, we also show that once patients are transplanted, their prognosis is good in almost every European country.

The effect of macroeconomics on access to kidney transplantation

We found large variation in access to kidney transplantation between European countries. In line with previous studies, we demonstrate that country wealth forms the strongest determinant of access to kidney transplantation[4,8], explaining 67% of the variation in transplantation rates between countries. This suggests that poorer countries may lack financial resources and/or experience to provide the expensive and complex transplantation care.[4] As a consequence, children with ESKD in these countries remain longer on dialysis. Although morbidity and mortality are much higher on dialysis than after kidney transplantation,[2] there is some evidence that a short period of dialysis prior to transplantation has little effect on patient survival as compared with pre-emptive transplantation.[5,13] Nevertheless, given the better quality of life, cognitive development, and growth post-transplant,[2] and taking into account the higher cost-effectiveness associated with transplantation compared with dialysis,[14,15] lower income countries in Europe would benefit financially, and in "healthy" life-years gained, by transplanting these children sooner. Also, for some higher income countries in Europe transplant activities could be improved, as the access to transplantation is lower compared to other high-income countries.

The effect of patient age on access to kidney transplantation

We found that patient age increased the variation in kidney transplant rates across Europe by 14.5%. Kidney transplantation in the youngest patients is challenging, requiring the expertise of a

multidisciplinary team. Moreover, the surgical procedure is associated with several complications risking severe morbidity, graft loss, and even death.[16] Country differences in experience, expertise, and the availability of specialists may partly explain why countries vary in their ability to transplant the youngest children. For example in Finland, a country where many young patients require RRT due to a relatively high incidence of congenital nephrotic syndrome of the Finnish type, one would expect a lower access to kidney transplantation based on the patient age distribution. However, here we show the opposite, finding higher transplantation rates for Finland despite their complex patient population. Subsequently, Finland contributes to an increase in the variation between countries regarding access to transplantation after adjustment for patient age.

Other potential determinants of access to kidney transplantation

Other factors such as donor consent policy, donor type, sex, and PRD distribution explained little of the variation in access to pediatric kidney transplantation between European countries. This is a registry study, with limited set of variables, so several kidney transplantation-related factors that may have contributed to a country's ability to transplant pediatric patients are unavailable. Previous studies showed that differences in kidney transplantation policies, such as recommendations regarding living or deceased donation, the maximum accepted donor age, cold ischemia time, minimum accepted recipient age, and HLA-matching, may also play a role in explaining country differences in access to transplantation,[4,11] along with various cultural, local, and logistic factors.[17] All these factors may partly explain the variation in access to kidney transplantation, and their absence in our analyses may have led to some degree of residual confounding.

Kidney graft failure

Despite the disparities found in access to kidney transplantation, 5-year graft failure rates were relatively similar across Europe, with only a few countries demonstrating graft failure rates above or below the European average. This variation was amplified after taking country differences in Gross

Domestic Product (GDP) and donor-type distribution into account, although the overall variation remained small. We postulate two main explanations for the lack of variation in country graft failure rates.

First, we found a strong association between national wealth and access to transplantation, but not between national wealth and graft failure rate. Similarly, in previous registry studies we have shown that lower country wealth goes together with lower access to RRT, and higher mortality risk on RRT.[4,7,8] This suggests a selection process favoring the healthiest patients in lower income countries; patients must first be accepted on dialysis, then survive long enough to be able to receive a kidney transplant, and lastly, be selected for transplantation. Also, the proportion of kidneys donated by living donors in low income countries was higher than in middle- and high-income countries, and surprisingly in the lower income countries a lower proportion of kidneys donated by living donors was associated with a higher likelihood of receiving a kidney transplant. These findings further emphasize the selection process in poorer countries. In contrast, in wealthier countries, where we have shown that the majority of patients are accepted on RRT, and where mortality rates are relatively low, selection is limited as most children with ESKD actually have access to transplantation. This selection process in low- and middle-income countries is therefore likely to attenuate differences in estimates of graft failure rate across Europe and adjusting for GDP would increase the variation in graft failure across countries. Overall, the variation in graft failure between individual European countries remained small, a finding that is strengthened by our sensitivity analyses comparing the graft failure rates against rates obtained in high-income countries as a proxy for best practice. Only a small minority of countries showed graft failure rates that were significantly higher than the average rate among high-income countries.

Second, the high kidney graft survival rates across Europe may be explained by excellent access to immunosuppressive medications for all pediatric patients, combined with full insurance coverage

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(personal communication NC Chesnaye[S1]).[18–20] This premise is supported by a study in US adults, where income-related differences in graft survival seemed to disappear if life-time coverage of immunosuppressive medication is provided.[21] Moreover, in a previous comparison between Europe and the US, Gondos et al. showed a lower 5-year graft survival of deceased donor kidneys in all racial groups in the US (74.5% in white, 56.8% in African, and 74.4% in Hispanic pediatric patients) compared with Europe (83.6%).[22] These differences could not be attributed to differences in patient characteristics. As long-term insurance coverage for immunosuppressive medication was limited in the US, but unrestricted in Europe, the authors suggested that differences in insurance coverage of immunosuppressive medication may be responsible.[22]

Compared with other continents, the European five-year graft survival (88.3% and 88.8% in high-income countries) was slightly higher than reported in registry studies from Australia and New Zealand (83%), and the US (86.4% for living donor kidneys, and 79.2% for deceased donor kidneys).[23,24] By contrast, the outcomes of pediatric kidney transplantation in developing countries were much more variable, and the 5-year graft survival varied from 44% in South Africa to 92% in Saudi Arabia. Social, logistical, and economical issues, such as the inability to afford immunosuppressive medication, form major challenges in developing countries.[25]

Strengths and limitations

An important strength of our study is the availability of up-to-date kidney allograft failure rates for almost all pediatric kidney transplant recipients across Europe. However, several limitations of our work need to be acknowledged. The ESPN-ERA/EDTA-Registry only collects data on patients receiving RRT. Therefore, information on patients with ESKD not (yet) receiving RRT is unavailable. As mentioned above, selection of the least sick patients for kidney transplantation may have introduced some degree of bias to our results. Furthermore, the Registry collects only limited data on the clinical condition of the patients, such as comorbidities, hospitalization, infection rates, reasons for graft

failure, as well as detailed transplant-related characteristics such as immunosuppression, HLA-matching, and donor characteristics. These factors may be important for explaining the variation in graft survival, which may have led to some degree of residual confounding.

Conclusion

Large disparities exist in access to pediatric kidney transplantation across Europe, whereas graft survival rates are relatively similar. As kidney transplantation is associated with lower morbidity and mortality, and is more cost-effective[14,15] compared with dialysis,[2] substantial health gains could be achieved by improving access to kidney transplantation, especially in low- and middle-income countries. Strategies advocated to promote early kidney transplantation include the introduction of living donation programs and the adoption of a pediatric priority policy.[4,14,15]

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Methods

Data source and study population

On an annual basis, the European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry collects data from 37 European countries on all children receiving RRT in Europe.[26] For this study, we included data for all patients (<20 years old) who started RRT between January 1, 2007, and December 31, 2015, on country, age at onset of RRT, sex, PRD, initial treatment modality, (pre-emptive) transplantation, mortality, and graft failure.[26] Information on whether kidneys came from heart beating or non-heart beating deceased donors was not available. PRDs were categorized following the ERA-EDTA coding system adapted for children.[27] As some of these groups comprise small numbers of patients, we further categorized the groups ischemic renal failure, hemolytic uremic syndrome, metabolic disorders, vasculitis and miscellaneous as 'miscellaneous'. Due to the non-linear relationship between patient age and graft failure,[28] patients were divided into clinically relevant age groups: 0 to <2 years, 2 to <6 years, 6 to <13 years and ≥ 13 years. To avoid underestimation of the graft failure rate, it was necessary to exclude Italy, as in that country data on kidney transplantation was lacking. Germany was also excluded as data from dialysis and transplant centers were provided separately, and linkage between the two sources was not possible. Cyprus, Latvia, Moldova, and Montenegro were excluded due to follow-up periods shorter than 5 years. For several other countries, data was only provided for part of the study period (Table S2). Patients with unknown initial treatment modality were excluded from the analyses (n = 120). No other values were missing for patient-related variables and analyses were restricted to complete cases only.

GDP and health expenditure per capita were extracted from the World Bank database[29] and averaged over the study period for each country. Based on mean GDP, countries were categorized by tertiles into low-, middle-, and high-income (Table S3). The country policy for donor consent (presumed or informed) was extracted from a previous ESPN/ERA-EDTA Registry study[4] and, if

missing from this study, obtained through personal communication with the national registry representative of those countries (Supplementary Appendix).[S2,S3]

Statistical analyses

Access to kidney transplantation was assessed using the cumulative incidence competing risk (CICR) method[30] to calculate the time from RRT initiation to first transplantation, with death prior to transplantation as a competing risk. In addition, the 5-year kidney transplantation rate was calculated for each country as the number of first transplantations divided by the time on RRT using Poisson regression.

The 5-year probability of kidney graft survival was studied using CICR plots, and was defined as being alive with a functioning graft. Crude 5-year graft failure rate was calculated for each country as the number of graft failures divided by the number of patient years at risk using Poisson regression.

Similarly, the five-year European average kidney transplantation and graft failure rates were calculated as the overall number of transplants performed or overall number of graft failures divided by the overall number of patient follow-up years. We compared the crude kidney transplantation and graft failure rate for each country against the average European rates using spine plots.[31] This allows identification of countries that fall outside the 95% and 99% control limits (approximately 2 and 3 standard deviations (SD), respectively), as performing either better or worse compared to the European average. The control limits indicate the expected limits of random deviation from the European transplant or graft failure rate and were calculated by assuming that the number of events in a country followed a Poisson distribution.[31]

We hypothesized causal pathways using directed acyclic graphs for the determinants of access to kidney transplantation and graft failure based on existing literature and expert opinion (Figure S5). Following these graphs and the criteria for confounding,[32] we applied Cox proportional hazards regression with country modelled as a random effect to study potential determinants of access to

transplantation and graft failure. In the empty or baseline model without any determinants, the random effect provides an estimate for the variation in outcome between countries. To assess the impact of each determinant on this estimate, we added the determinant of interest to the baseline model and calculated the proportional change in variance (PCV) by subtracting the adjusted variance from the baseline variance and dividing it by the baseline variance. This allows examination of the effect of an explanatory factor on the country variation in access to transplantation or graft failure.

As the transition to adult nephrology care occurs from the age of 15 years in some countries, we performed a sensitivity analysis excluding all patients above the age of 15 years at the start of RRT to test whether this potentially biased our results. The findings were similar to the main results and are therefore presented in the Supplementary Material (Tables S4 and S5).

Additionally, we also performed sensitivity analyses exploring the effect of different markers for income inequalities across countries. First, we explored the effect of the GINI coefficient, a statistical value representing income or wealth inequality. A GINI of zero expresses perfect equality, whereas a GINI of 100% represents maximum inequality. Similarly, we compared the access to transplantation and risk for graft failure based on the percentage of national wealth spent on health care. Both markers were obtained from the World Bank Database[29] and categorized into tertiles. Furthermore, as the aim of the European health policy framework is to achieve equity of access to high quality care,[6] instead of benchmarking kidney transplantation and graft failure against the European average, we also compared the rates in individual countries against the 'best outcomes'. As a proxy for best outcome we used the levels achieved in high-income countries (except for Spain in the analyses on graft failure due to a substantially higher graft failure rate than the other high-income countries).

Analyses were performed using SAS 9.4 statistical software package (SAS Institute, Cary, NC, USA).

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Disclosures

AMM reported financial activities parallel to his medical activity in the Spanish public state; RG reported travel support from a commercial sponsor to attend the ESPN Annual Meeting in 2018; JH reported consulting fees/paid advisory board from Astellas, lecture fees from Fresenius and Baxter, and current grant support from Augustinus Fond; TJ reported current grant support from Helsinki and Uusima Hospital District; SDM reported current institutional grant support from Astellas and Novartis for RCTs; BT reported consulting fees/paid advisory boards by Bristol-Myers, Squibb, Novartis and Raptor, travel support by Astellas and Novartis, and current grant support by Novartis; KJJ reported lecture fees from Fresenius Medical Care.

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Supplementary Material

Tables

Table S1a: Hazard ratios of access to transplantation and the effect on the variance between countries for the determinants GINI index and health expenditure expressed as percentage of GDP.

Table S1b: Hazard ratios of graft failure and the effect on the variance between countries for the determinants GINI index and health expenditure expressed as percentage of GDP.

Table S2: Countries and years contributing to the ESPN/ERA-EDTA Registry

Table S3: General information by country, stratified according to income group

Table S4: Hazard ratios of determinants of access to kidney transplantation and the effect of each determinant on the variance between countries among patients < 15 years of age (sensitivity analysis)

Table S5: Hazard ratios of determinants of kidney graft failure and the effect of each determinant on the variance in graft failure between countries among patients < 15 years of age (sensitivity analysis)

Figure legends

Figure S1: Country random effects and five-year access to kidney transplantation.
Abbreviations: HR, Hazard Ratio; GDP, Gross Domestic Product.

Figure S2: Country random effects and five-year graft failure after kidney transplantation.
Abbreviations: HR, Hazard Ratio; GDP, Gross Domestic Product.

Figure S3: Spine plot of five-year kidney transplantation rates by country compared to average rate in high-income countries.
Number of kidney transplantations per 1000 patient-years of follow-up per country.
Rates in the grey segment are not statistically significantly different from the average in high-income countries. The pink and blue segments represent the control limits (95% and 99% control limits, corresponding to approximately 2 and 3 standard deviations), which indicate the range in which transplant rates are expected to fall based on random deviation.
Rates in the pink segments are significantly lower, and rates in the blue segments are significantly higher than the average rate in high-income countries.

Figure S4: Spine plot of five-year kidney graft failure rate by country compared to the average rate in high-income countries.
Number of graft failures per 1000 patient-years of follow-up per country. Rates in the grey segment are not statistically significantly different from the average of high-income countries. The pink and blue segments represent the control limits (95% and 99% control limits, corresponding to approximately 2 and 3 standard deviations), which indicate the range in which graft failure rates are expected to fall based on random deviation. Rates in pink segments are significantly higher, and rates in the blue segments are significantly lower than the average in high-income countries.

Figure S5: Directed Acyclic Graph (DAG) describing the causal pathways of kidney transplantation in children.
Abbreviations: GDP, Gross Domestic Product; PRD, primary renal disease.

Supplementary references for personal communication

Supplementary information is available at Kidney International's website.

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Table 1: Patient characteristics

		Total population n=6909	Low income* n=1960 (28.4%)	Middle income* n=1118 (16·2%)	High income* n=3831 (55·4%)
Baseline RRT population					
Male sex	N (%)	4001 (57.9)	1087 (55.4)	647 (57.9)	2267 (59.2)
Age at start of **RRT** (years)	N (%)				
0 to < 2		932 (13.5)	205 (10.5)	180 (16.1)	547 (14.3)
2 to < 6		952 (13.8)	247 (12.6)	125 (11.2)	580 (15.1)
6 to < 13		2170 (31.4)	762 (38.9)	359 (32.1)	1049 (27.4)
≥ 13		2855 (41.3)	746 (38.1)	454 (40.6)	1655 (43.2)
Primary renal disease	N (%)				
CAKUT[1]		2453 (33.5)	712 (36.3)	339 (30.3)	1402 (36.6)
Glomerulonephritis		1153 (16.7)	351 (17.9)	198 (17.7)	604 (15.8)
Cystic kidney disease		728 (10.5)	196 (10.0)	148 (13.2)	384 (10.0)
Hereditary nephropathy		441 (6.4)	59 (3.0)	72 (6.4)	310 (8.1)
Miscellaneous		1408 (20.4)	417 (21.3)	251 (22.5)	740 (19.3)
Missing/Unknown		726 (10.5)	225 (11.5)	110 (9.8)	391 (10.2)
Initial treatment modality	N (%)				
Hemodialysis		3015 (43.6)	1000 (51.0)	438 (39.2)	1577 (41.6)
Peritoneal dialysis		2547 (36.9)	760 (38.8)	572 (51.2)	1215 (31.7)
Kidney transplantation		1324 (19.2)	184 (9.4)	106 (9.5)	1034 (27.0)
Deceased donor		478 (6.9)	30 (1.5)	39 (3.5)	409 (10.7)
Living donor		796 (11.5)	125 (6.4)	62 (5.5)	609 (15.9)
Missing donor type		50 (0.7)	29 (1.5)	5 (0.4)	16 (0.4)
Unknown dialysis		23 (0.3)	16 (0.8)	2 (0.2)	5 (0.1)
Baseline transplanted population					
Age at transplantation (years)	N (%)				
0 to < 2		155 (3.9)	28 (3.7)	8 (1.2)	119 (4.1)
2 to < 6		804 (18.6)	99 (13.2)	100 (15.2)	605 (20.7)
6 to < 13		1429 (33.0)	301 (40.0)	242 (36.8)	886 (30.4)
≥ 13		1938 (44.8)	324 (43.1)	307 (46.7)	1307 (44.8)

* Low-income countries: Albania, Belarus, Bosnia and Herzegovina, Bulgaria, FYR of Macedonia, Georgia, Romania, Russia, Serbia, Turkey, and Ukraine; Middle-income countries: Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Poland, Portugal, Slovakia, and Slovenia; High-income countries: Austria, Belgium, Denmark, Finland, France, Iceland, Spain, Sweden, Switzerland, the Netherlands, Norway, and United Kingdom.
Abbreviations: [1] Congenital anomalies of the kidney and urinary tract;

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Table 2: Hazard ratios for access to kidney transplantation and the effect of each determinant on the variance between countries

	Unadjusted hazard ratio (95% CI)	P-value	Confounders*	Adjusted hazard ratio (95% CI)	P-value	Additionally adjusted for GDP	P-value	Variance (SE)	Proportional change in variance
Baseline model								0.34 (0.09)	
Macro-economics									
[1] Income group								0.11 (0.04)	-66.6%
Low income	0.35 (0.26-0.48)	<0.001				-			
Middle income	0.48 (0.36-0.66)	<0.001				-			
High income	1.00 (reference)	-				-			
[2] Health expenditure (per 1000 USD)	1.19 (1.12-1.26)	<0.001				1.04 (0.93-1.17)	0.49	0.14 (0.04)	-58.5%
Legislation									
[3] Donor consent								0.32 (0.09)	-3.9%
Presumed	1.00 (reference)	-				1.00	-		
Informed	0.80 (0.53-1.20)	0.28				0.93 (0.70-1.24)	0.63		
[4] % Living donor								0.36 (0.10)	+6.2%
< 29.8%	1.07 (0.64-1.77)	0.80				1.06 (0.74-1.52)	0.76		
29.8 < 57.7%	0.95 (0.56-1.62)	0.85				0.80 (0.58-1.10)	0.17		
≥ 57.7%	1.00 (reference)	-				1.00 (reference)	-		
Patient characteristics									
[5] Age at start of RRT								0.38 (0.10)	+14.5%
0 to < 2	0.54 (0.49-0.59)	<0.001	2,6, 7	0.49 (0.45-0.54)	<0.001	0.49 (0.45-0.54)	<0.001		
2 to < 6	0.98 (0.90-1.08)	0.71		0.96 (0.88-1.05)	0.39	0.96 (0.88-1.05)	0.39		
6 to < 13	1.11 (1.04-1.19)	0.003		1.09 (1.01-1.16)	0.02	1.09 (1.01-1.17)	0.02		
≥ 13	1.00 (reference)	-		1.00 (reference)		1.00 (reference)	-		
[6] Sex								0.34 (0.09)	+0.2%
Female	0.95 (0.90-1.01)	0.10				0.95 (0.90-1.01)	0.10		
Male	1.00 (reference)	-							
[7] Primary renal disease								0.34 (0.09)	+1.7%
CAKUT[1]	1.00 (reference)	-	2,5,6	1.00 (reference)	-	1.00 (reference)	-		
Glomerulonephritis	0.81 (0.74-0.88)	<0.001		0.73 (0.67-0.80)	<0.001	0.73 (0.67-0.80)	<0.001		
Cystic kidney disease	1.16 (1.05-1.28)	0.003		1.11 (1.01-1.23)	0.03	1.11 (1.01-1.23)	0.03		
Hereditary nephropathy	0.85 (0.76-0.96)	0.01		0.85 (0.67-0.96)	0.009	0.85 (0.75-0.96)	0.009		
Miscellaneous	0.79 (0.73-0.86)	<0.001		0.78 (0.72-0.85)	<0.001	0.78 (0.72-0.85)	<0.001		
Missing/Unknown	0.87 (0.78-0.97)	0.01		0.80 (0.71-0.88)	<0.001	0.80 (0.71-0.89)	<0.001		

Abbreviations: [1]Congenital anomalies of the kidney and urinary tract;
*Confounders are labeled from [1] to [7] in the first column

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Table 3: Hazard ratios for kidney graft failure and the effect of each determinant on the variance in graft failure between countries

	Unadjusted hazard ratio (95% CI)	P-value	Confounders	Adjusted hazard ratio (95% CI)	P-value	Variance (SE)	Proportional change in variance
Baseline model						0.17 (0.09)	
Macro-economics							
[1] Income group						0.20 (0.10)	+21.1%
Low income	0.96 (0.52-1.77)	0.89					
Middle income	1.27 (0.73-2.20)	0.40					
High income	1.00 (reference)	-					
[2] Health expenditure (per 1000 USD)	0.96 (0.88-1.06)	0.44				0.17 (0.09)	+2.7%
Type of kidney transplantation							
[3] Timing of kidney transplantation						0.16 (0.08)	-6.5%
Pre-emptive	0.61 (0.47-0.79)	<0.001	2, 5	0.63 (0.49-0.81)	<0.001		
Non pre-emptive	1.00 (reference)	-		1.00 (reference)	-		
[4] Donor type						0.20 (0.10)	+18.4%
Deceased	1.00 (reference)	-	2	1.00 (reference)	-		
Living	0.57 (0.45-0.73)	<0.001		0.57 (0.45-0.73)	<0.001		
Unknown	1.49 (0.88-2.50)	0.14		1.48 (0.88-2.51)	0.14		
Patient characteristics							
[5] Age at kidney transplantation (years)						0.18 (0.09)	+7.4%
0 to < 2	1.63 (1.02-2.62)	0.04	2, 6, 7	1.71 (1.06-2.75)	0.03		
2 to < 6	1.15 (0.87-1.53)	0.33		1.18 (0.88-1.57)	0.26		
6 to < 13	0.90 (0.70-1.17)	0.43		0.88 (0.68-1.14)	0.35		
≥ 13	1.00 (reference)	-		1.00 (reference)	-		
[6] Sex						0.17 (0.09)	0.0%
Female	0.99 (0.80-1.23)	0.96					
Male	1.00 (reference)	-					
[7] Primary renal disease						0.16 (0.08)	-7.9%
CAKUT[1]	1.00 (reference)	-	2, 5, 6	1.00 (reference)	-		
Glomerulonephritis	1.48 (1.11-1.98)	0.008		1.52 (1.13-2.04)	0.005		
Cystic kidney disease	0.83 (0.57-1.21)	0.33		0.85 (0.58-1.24)	0.40		
Hereditary nephropathy	0.76 (0.46-1.26)	0.29		0.73 (0.44-1.22)	0.23		
Miscellaneous	1.17 (0.87-1.56)	0.29		1.20 (0.90-1.61)	0.22		
Missing/Unknown	0.81 (0.51-1.29)	0.38		0.83 (0.52-1.34)	0.45		

[1] Congenital anomalies of the kidney and urinary tract;

*Confounders are labeled from [1] to [7] in the first column

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Figure legends

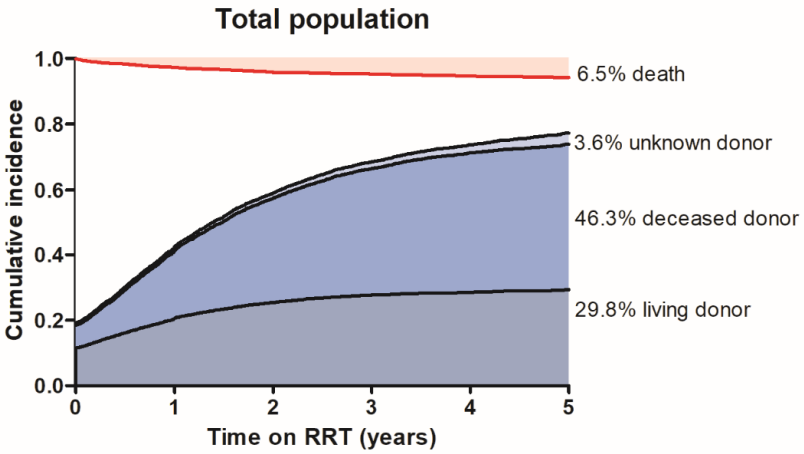
Figure 1. Cumulative incidence of receiving a kidney transplant according to donor type and adjusted for the competing event (death) in the first five years after initiating renal replacement therapy stratified by income group.

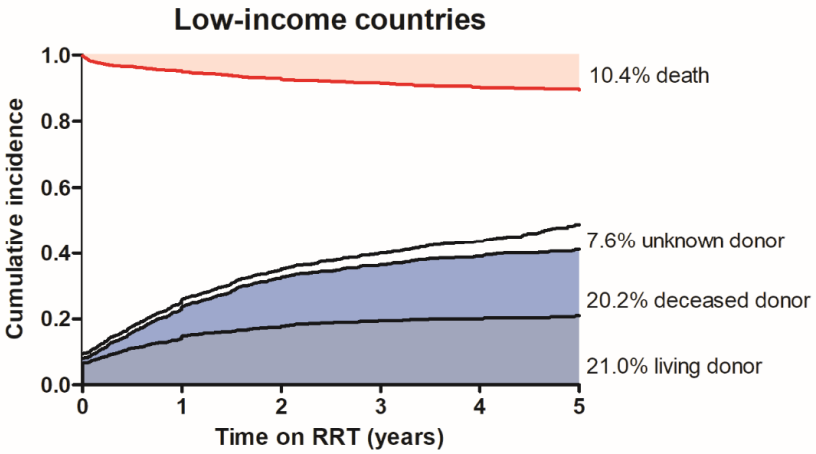
Figure 2: Spine plot of five-year kidney transplantation rates by country.
Number of kidney transplantations per 1000 patient-years of follow-up per country.
Rates in the grey segment are not statistically significantly different from the European average. The pink and blue segments represent the control limits (95% and 99% control limits, corresponding to approximately 2 and 3 standard deviations), which indicate the range in which transplant rates are expected to fall based on random deviation.
Rates in the pink segments are significantly lower, and rates in the blue segments are significantly higher than the European average rate.

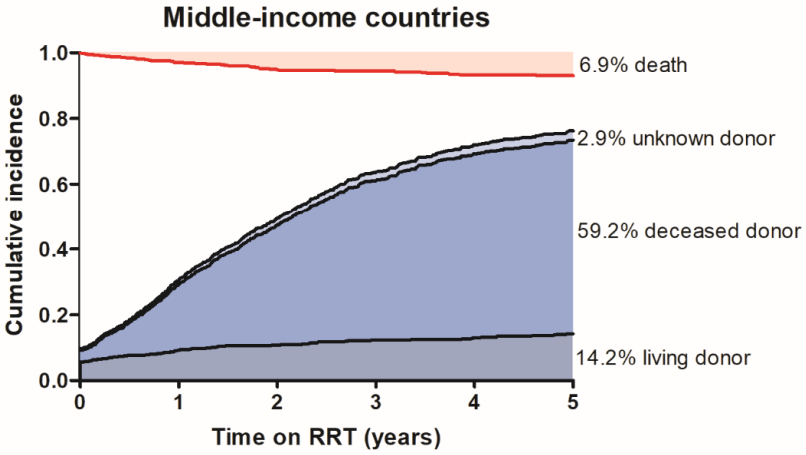
Figure 3. Cumulative incidence of graft failure and death five years after transplantation stratified by income group.

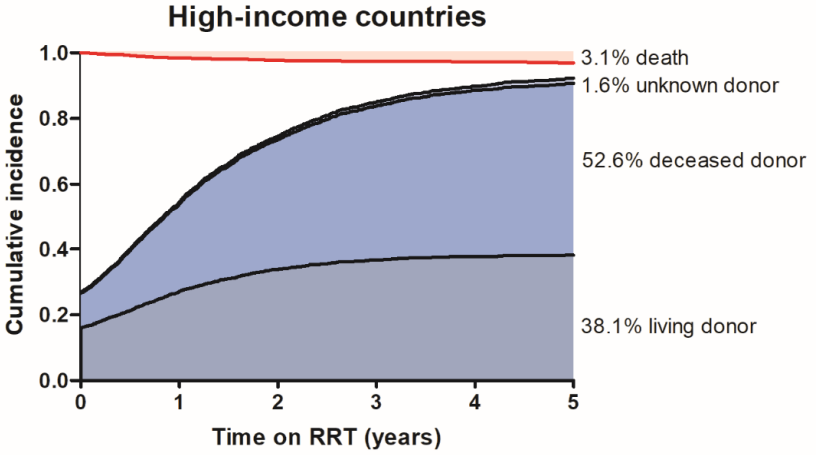
Figure 4: Spine plot of five-year kidney graft failure rate by country.
Number of graft failures per 1000 patient-years of follow-up per country. Rates in the grey segment are not statistically significantly different from the European average. The pink and blue segments represent the control limits (95% and 99% control limits, corresponding to approximately 2 and 3 standard deviations), which indicate the range in which graft failure rates are expected to fall based on random deviation. Rates in pink segments are significantly higher, and rates in the blue segments are significantly lower than the European average.

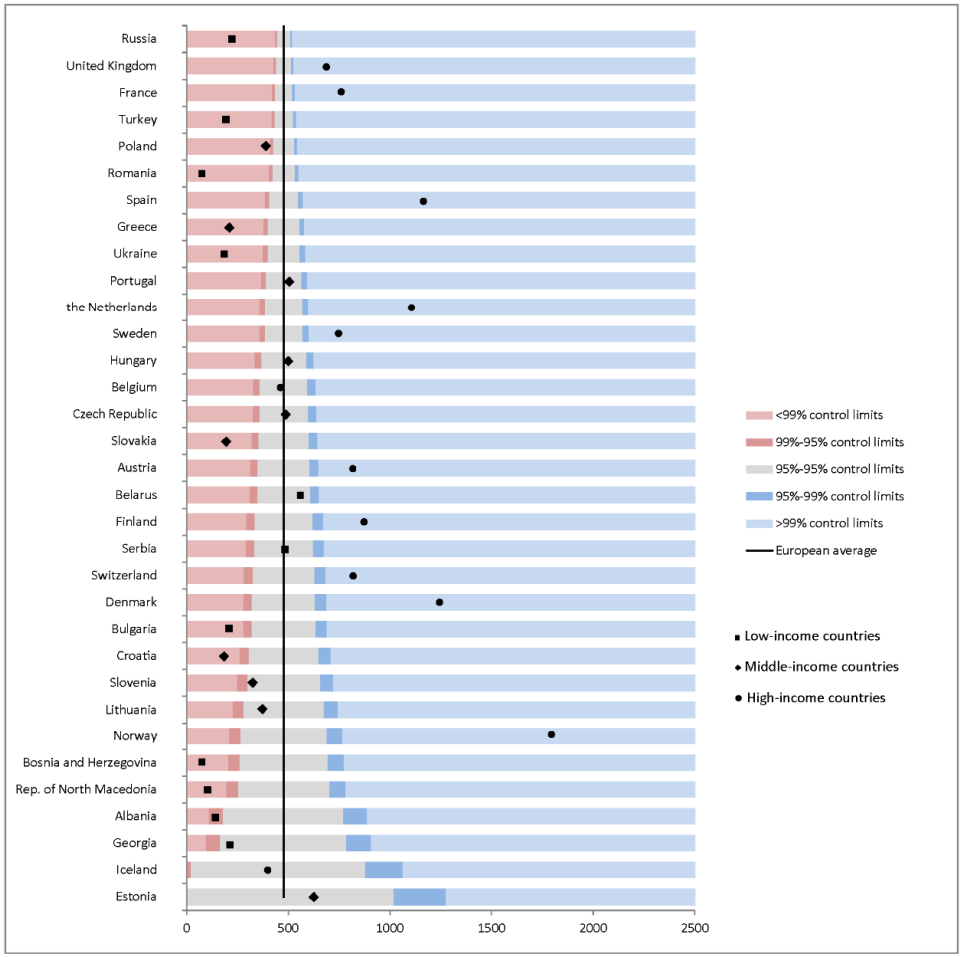
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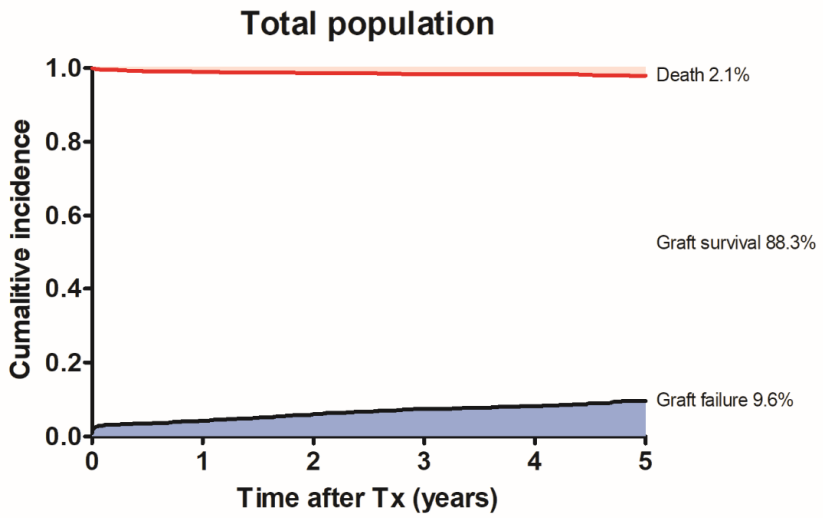

Total population
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time on RRT (years)
6.5% death
3.6% unknown donor
46.3% deceased donor
29.8% living donor

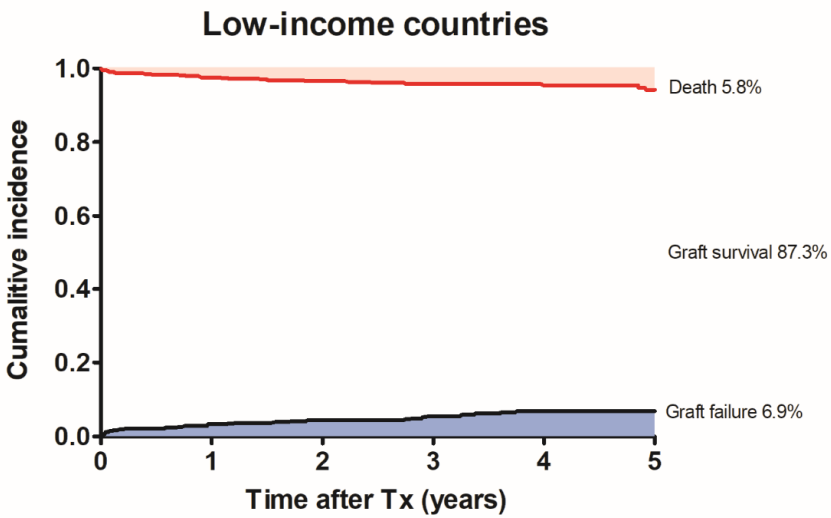

Low-income countries
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time on RRT (years)
10.4% death
7.6% unknown donor
20.2% deceased donor
21.0% living donor

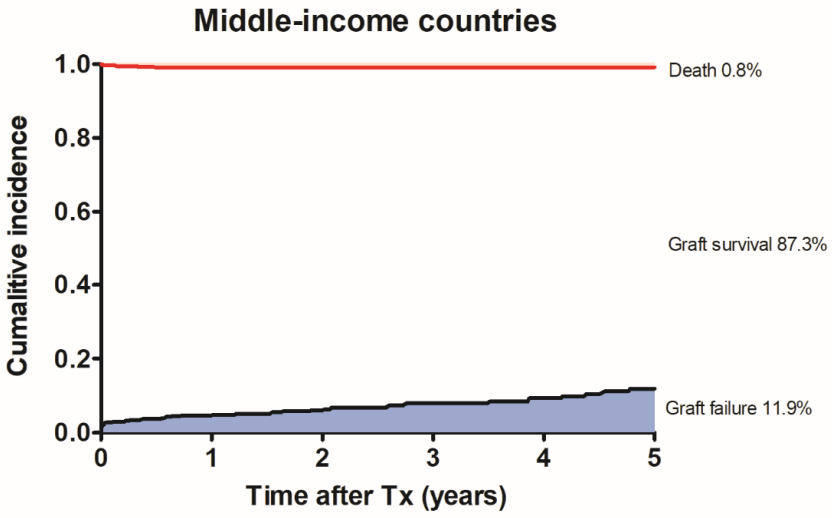

Middle-income countries
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time on RRT (years)
6.9% death
2.9% unknown donor
59.2% deceased donor
14.2% living donor

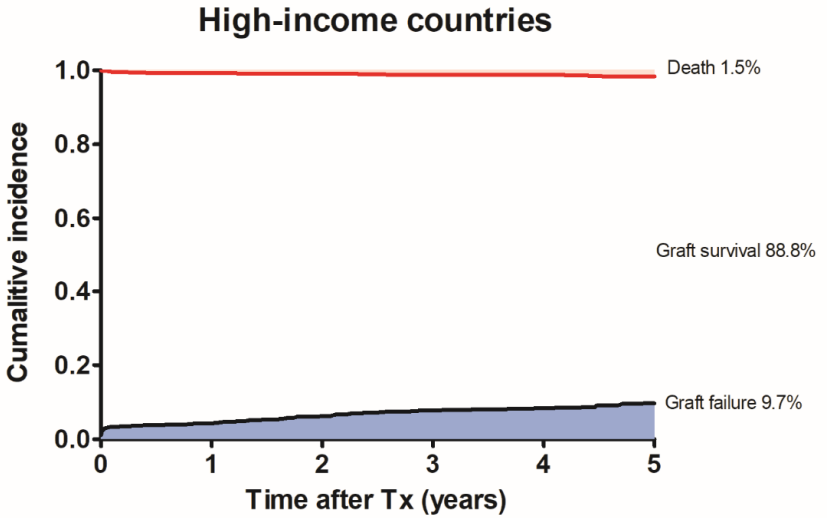

High-income countries
Cumulative incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time on RRT (years)
3.1% death
1.6% unknown donor
52.6% deceased donor
38.1% living donor

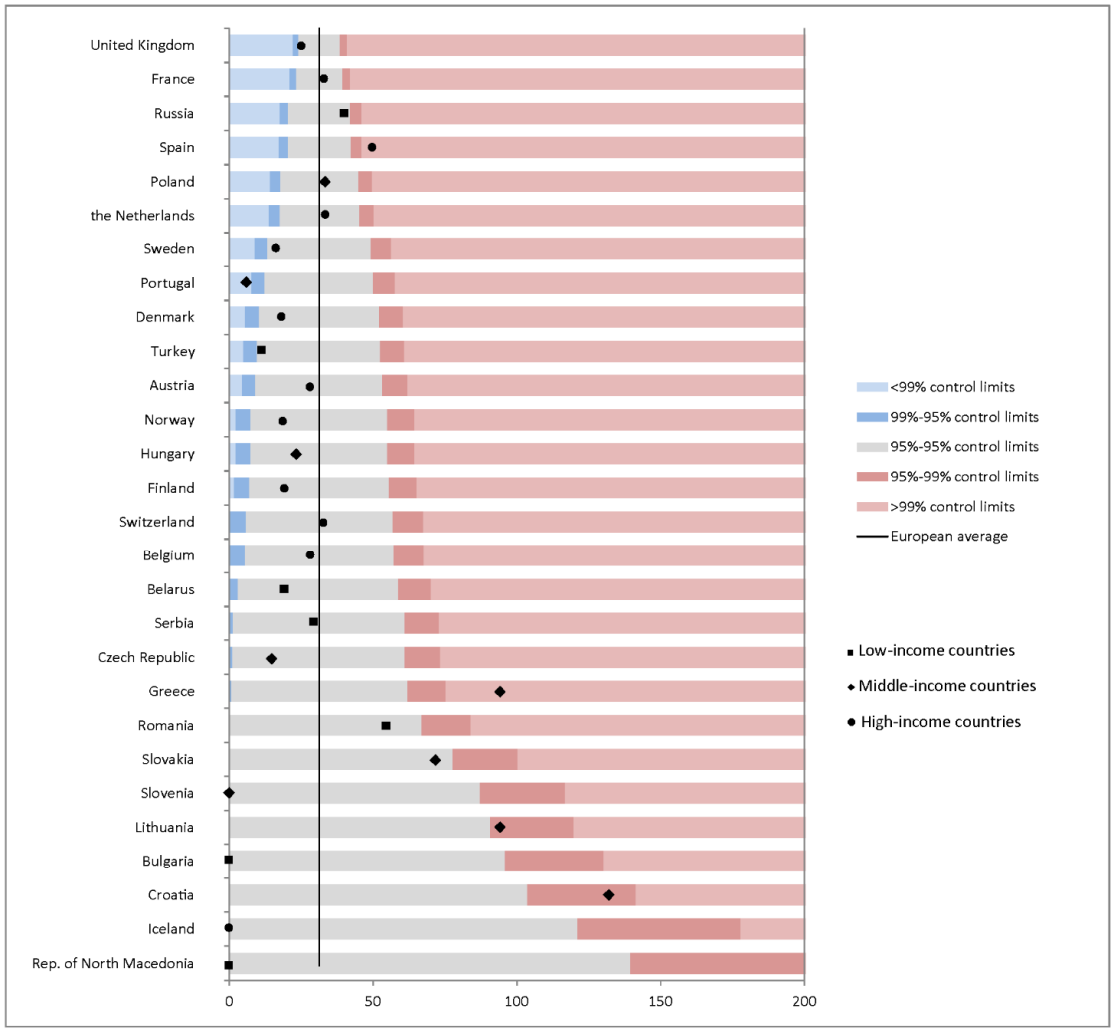

Russia
United Kingdom
France
Turkey
Poland
Romania
Spain
Greece
Ukraine
Portugal
the Netherlands
Sweden
Hungary
Belgium
Czech Republic
Slovakia
Austria
Belarus
Finland
Serbia
Switzerland
Denmark
Bulgaria
Croatia
Slovenia
Lithuania
Norway
Bosnia and Herzegovina
Rep. of North Macedonia
Albania
Georgia
Iceland
Estonia
0
500
1000
1500
2000
2500
<99% control limits
99%-95% control limits
95%-95% control limits
95%-99% control limits
>99% control limits
European average
Low-income countries
Middle-income countries
High-income countries


Total population
Cumulitive incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time after Tx (years)
Death 2.1%
Graft survival 88.3%
Graft failure 9.6%


Low-income countries
Cumulitive incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time after Tx (years)
Death 5.8%
Graft survival 87.3%
Graft failure 6.9%


Middle-income countries
Cumulitive incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time after Tx (years)
Death 0.8%
Graft survival 87.3%
Graft failure 11.9%


High-income countries
Cumulitive incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Time after Tx (years)
Death 1.5%
Graft survival 88.8%
Graft failure 9.7%


United Kingdom
France
Russia
Spain
Poland
the Netherlands
Sweden
Portugal
Denmark
Turkey
Austria
Norway
Hungary
Finland
Switzerland
Belgium
Belarus
Serbia
Czech Republic
Greece
Romania
Slovakia
Slovenia
Lithuania
Bulgaria
Croatia
Iceland
Rep. of North Macedonia
0
50
100
150
200
<99% control limits
99%-95% control limits
95%-95% control limits
95%-99% control limits
>99% control limits
European average
Low-income countries
Middle-income countries
High-income countries