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Original Article

ORIGINAL ARTICLE

Disparities in treatment and outcome of kidney replacement therapy in children with comorbidities: an ESPN/ERA Registry study

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ABSTRACT

Background. Data on comorbidities in children on kidney replacement therapy (KRT) are scarce. Considering their high relevance for prognosis and treatment, this study aims to analyse the prevalence and implications of comorbidities in European children on KRT.

Methods. We included data from patients <20 years of age when commencing KRT from 2007 to 2017 from 22 European countries within the European Society of Paediatric Nephrology/European Renal Association Registry. Differences between patients with and without comorbidities in access to kidney transplantation (KT) and patient and graft survival were estimated using Cox regression.

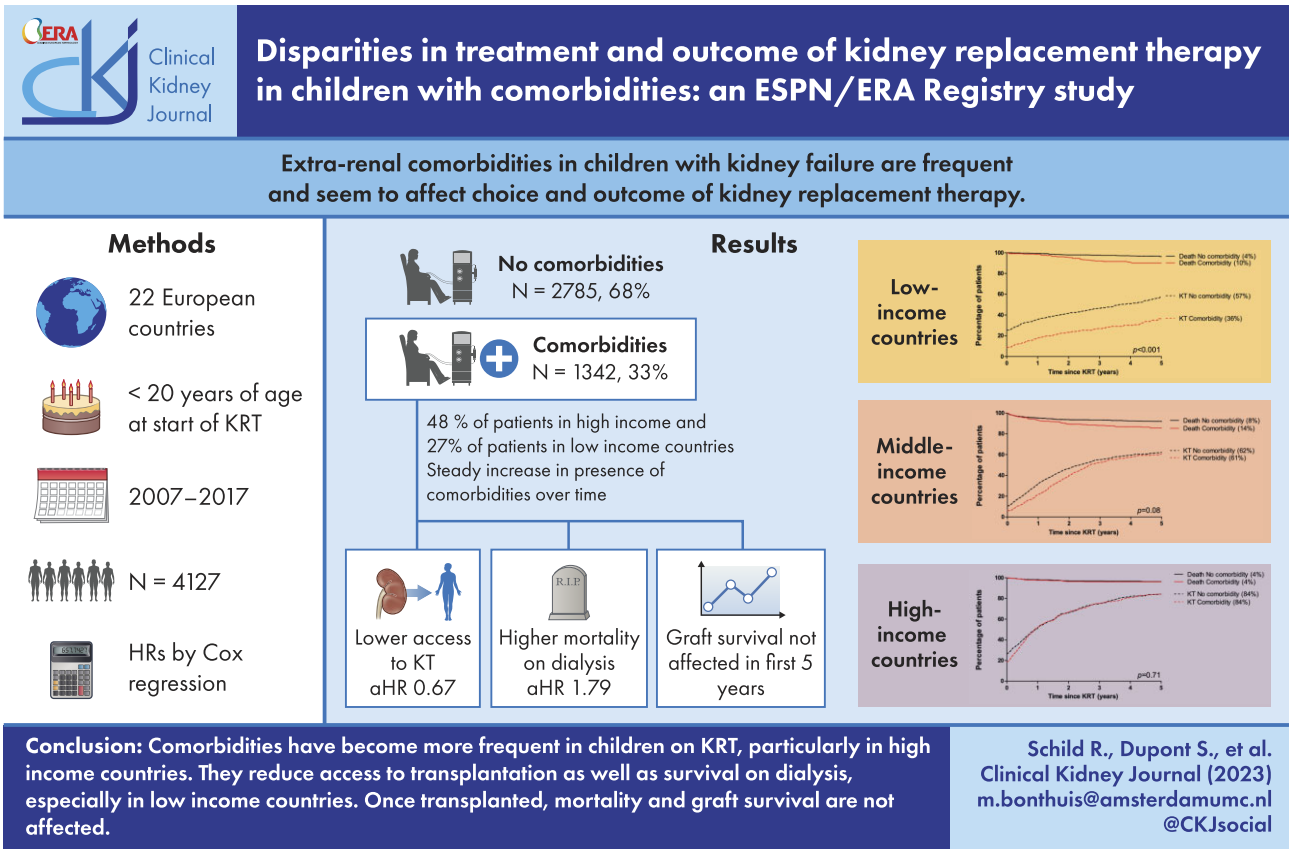
Results. Comorbidities were present in 33% of the 4127 children commencing KRT and the prevalence has steadily increased by 5% annually since 2007. Comorbidities were most frequent in high-income countries (43% versus 24% in low-income countries and 33% in middle-income countries). Patients with comorbidities had a lower access to transplantation {adjusted hazard ratio [aHR] 0.67 [95% confidence interval (CI) 0.61–0.74]} and a higher risk of death [aHR 1.79 (95% CI 1.38–2.32)]. The increased mortality was only seen in dialysis patients [aHR 1.60 (95% CI 1.21–2.13)], and not after KT. For both outcomes, the impact of comorbidities was stronger in low-income countries. Graft survival was not affected by the presence of comorbidities [aHR for 5-year graft failure 1.18 (95% CI 0.84–1.65)].

Conclusions. Comorbidities have become more frequent in children on KRT and reduce their access to transplantation and survival, especially when remaining on dialysis. KT should be considered as an option in all paediatric KRT patients and efforts should be made to identify modifiable barriers to KT for children with comorbidities.

LAY SUMMARY

Kidney transplantation (KT) is considered the optimal treatment for children who suffer from permanent kidney failure, because it leads to a lower mortality and higher quality of life compared with dialysis. Children on dialysis frequently suffer from diseases of other organs (comorbidities) that can directly lower their life expectancy and could potentially represent a barrier for transplantation, posing an additional disease burden for these children. In this study we looked at data from a large multinational registry for children with kidney failure who require kidney replacement. Using these data, we studied whether these children suffered from comorbidities and whether these impact their life expectancy or their access to KT. We found that more and more children with kidney failure suffer from comorbidities when starting kidney replacement therapy. We also found that these children have a lower access to KT and a higher mortality on dialysis compared with children without comorbidities, especially in low-income countries. After KT, children with comorbidities have a similar mortality and graft survival compared with children without comorbidities. We concluded that reduced access to a kidney transplant might represent a modifiable barrier to KT in children with comorbidities, especially in low-resource countries. We suggest that children with comorbidities in need for kidney replacement therapy should be rapidly evaluated for eligibility for KT.

GRAPHICAL ABSTRACT



Keywords: children, chronic kidney disease, comorbidities, epidemiology, kidney transplantation

INTRODUCTION

Paediatric patients with end-stage kidney disease (ESKD) requiring kidney replacement therapy (KRT) typically present with a complex medical condition bearing high morbidity and mortality. Extrarenal comorbidities are present in about one-third of paediatric KRT patients [1]. Comorbidities are known to have large implications on the management and prognosis of these patients and therefore pose further challenges for the clinician [1, 2].

In the adult KRT population, comorbidities are associated with higher mortality [3–5] and lower access to transplantation [6]. Comorbidity scores predictive for mortality and graft function [7, 8] help in providing adequate counselling for patients and their families.

In contrast to adult KRT patients, in the paediatric KRT population, little is known about the implications of different comorbidities on outcomes like access to kidney transplantation (KT) and patient and graft survival. With progress in medical and surgical treatment, survival of children with advanced chronic kidney disease (CKD) requiring KRT has significantly improved in recent decades [9–12]. This also resulted in changes in the demographics of the KRT population. Children with more complex conditions are now accepted into KRT programs [13, 14]. In a study from the International Pediatric Peritoneal Dialysis Network (IPPN), an association between the presence of comorbidities and higher hospitalization and mortality rates in children on peritoneal dialysis (PD) was reported [1].

Differences in the frequency and patterns of comorbidities between paediatric and adult ESKD patients, as well as limited information on the prevalence and burden of extrarenal comorbidities in children on KRT, indicate the importance of a more in-depth investigation in paediatric patients. Therefore, the aim of this study was to assess the impact of extrarenal comorbidities on access to KT and patient and graft survival in European paediatric KRT patients in order to guide future recommendations for the management of these patients.

METHODS

Data source and study population

On an annual basis, the European Society for Paediatric Nephrology/European Renal Association (ESPN/ERA) Registry collects data from 37 European countries on all children receiving KRT in Europe [15]. We included data from patients <20 years of age when commencing KRT between 1 January 2007 and 31 December 2017 from 22 European countries. We grouped countries into low, middle and high income according to their gross domestic product per capita (GDP) tertiles: Albania, Belarus, Bulgaria, Georgia, Republic of North Macedonia, Serbia and Turkey (low income); Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, Russia and Slovakia (middle income); and the Czech Republic, Greece, Ireland, Portugal, Slovenia, Spain and Switzerland (high income). GDP data were obtained from the World Bank database

[16]. Only countries covering the entire paediatric population on KRT (e.g. both dialysis and KT) were considered in the analyses.

The following parameters were collected for each subject: country, date of birth, sex, primary disease, treatment modality at the start of KRT and all (dates of) subsequent changes in treatment modalities, date and cause of death if applicable and the presence of comorbidities at KRT initiation. Comorbidities were defined as the presence of one or more medical conditions besides the primary kidney disease recorded at KRT initiation. The registry predefined 14 comorbidity categories. Additional ones were created when necessary, resulting in a total of 19 categories (Supplementary Table S1). A free-text field for further detailed description was available and entries were classified into the pre-existing categories. The presence of a particular comorbidity was coded as either 'yes', 'no', 'unknown' or missing. When information was missing, we assumed the patient did not have any comorbidity. Free-text comorbidities were further graded by severity (mild, severe, ungraded) based on expert opinion. Comorbidities were classified as severe if expected to lead to a significant and permanent impaired health status or an impairment of general life expectancy, such as syndromic disorders, cerebral palsy, severe neurodevelopmental disorders or malignancies. The cause of kidney failure was classified according to pre-existing ERA groups adapted for children and causes of death were defined by the ERA coding system [17].

Statistical analyses

Data were analysed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS statistical software package 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics were used to compare baseline characteristics between patient groups. We used the chi-squared test for categorical variables and the Kruskal–Wallis test for numerical variables.

Trends were studied using the JoinPoint regression program, as described previously [18]. Only countries contributing data for the entire time interval between 2007 and 2017 were included in the trend analysis.

Univariate patient and graft survival at 5 years was explored using Kaplan–Meier survival estimates. A cumulative incidence competing risks (CICR) model was used for access to KT, with death during dialysis as a competing event. CICR curves were compared with the Gray method [19]. For comparison of access to KT and patient and graft survival in different subgroups of comorbidities, hazard ratios (HRs) were calculated using Cox proportional hazards regression, including a frailty term for country. Furthermore, adjustment was made for possible confounding effects of sex, age at KRT initiation, primary kidney disease and country income category. For the analysis of graft survival, an additional adjustment was made for donor type. Additionally, we studied patient survival on dialysis, censoring patients at KT.

Five-year graft survival was defined as being alive with a functioning graft 5 years after KT. Additionally, we calculated death-censored graft survival.

In order to test for reporting bias concerning the aetiology of the comorbidities, we performed several sensitivity analyses. First, we repeated all analyses by excluding patients with acquired cardiovascular diseases, as these might be consequences of kidney failure rather than true pre-existing comorbidities and might therefore have a different impact on outcomes in the individual patient. In the main analyses, all patients with missing information regarding comorbidity status [$n = 1620$ (39%)] were assumed to be comorbid-free. In a second sensitivity analysis we included only patients with known information about their comorbidity status. Third, we repeated analyses assuming that patients with missing information on their comorbidity status suffered from at least one comorbidity. Moreover, we analysed associations with access to KT and patient and graft survival for the most prevalent comorbidity groups separately.

RESULTS

Baseline characteristics

We included 4127 children starting KRT between 2007 and 2017 in Europe. At least one comorbidity was present in about one-third of the patients (33%), of which 24% were classified as 'severe'(Table 1). Among patients with comorbidities, most patients had a single comorbidity (71%) and 28% had a congenital condition with an extrarenal manifestation. Multiple comorbidities were reported in 29% (Table 1).

The characteristics of our study population are shown in Table 2. Congenital anomalies of the kidney and urinary tract were the most common cause of kidney failure (34%). The median age at KRT start was 10.4 years [interquartile range (IQR) 5.1–14.1]. PD was the most frequent initial KRT modality in both groups. Pre-emptive transplantation was less often performed in comorbid (12%) than in non-comorbid patients (18%). Respectively, 52% and 56% of those pre-emptive transplants came from living donors.

Patients without comorbidities were more likely to be male, from a low-income country and to have haemolytic uremic syndrome (HUS) or congenital anomalies of the kidney and urinary tract (CAKUT) as primary kidney diseases. Patients with comorbidities were more likely to come from a high-income country and have cystic kidney disease, hereditary nephropathy or ischaemic renal failure as the primary kidney disease.

Subgroups and trend of comorbidities

The most common comorbidities were cardiovascular diseases (41%), followed by neurological and motor disorders (22%) and cognitive impairment (16%; Table 1). The prevalence of comorbidities steadily increased by 5% per year on average [95% confidence interval (CI) 3–7], from 26% in 2007 to 42% in 2017 (Fig. 1). There were no significant changes in severity grade or any specific subgroup of comorbidity over the study period.

Access to KT

During the first 5 years since KRT start, a total of 2318 patients (56%) received a first KT. Among patients with comorbidities, 54% received a KT compared with 57% of children without comorbidities. In contrast, 9% of the patients with comorbidities and 6% of the patients without comorbidities died on dialysis prior to receiving a KT.

The median age at KT was 11.8 years (IQR 7.0–14.8), with no statistical differences between patients with or without comorbidities. Living donor transplantation was less frequently performed in patients with comorbidities (29% versus 37%; Supplementary Table S1).

Overall unadjusted access to KT was slightly lower in patients with than without comorbidities. However, lower access to KT among patients with comorbidities was most pronounced in low-income countries, as shown by competing risk analysis stratified by GDP income categories (Fig. 2). This was the case for all major groups of comorbidities (Supplementary Table S5A).

Table 1: Patients by comorbidity category.

Specifications of comorbidities	Total, N (%)	Low-income countries, n (%)	Middle-income countries, n (%)	High-income countries, n (%)
Comorbidities				
1	950 (71)	218 (69)	309 (69.9)	423 (72.6)
2	260 (19)	65 (21)	92 (20.8)	103 (17.7)
≥3	132 (10)	34 (11)	41 (9.3)	57 (9.8)
Severity				
Mild	100 (8)	17 (5)	17 (3.8)	66 (11.3)
Ungraded	917 (68)	214 (68)	331 (74.9)	372 (63.8)
Severe	325 (24)	86 (27)	94 (21.3)	145 (24.9)
Categories[a]				
Cardiovascular disease	552 (41)	72 (16)	144 (33)	336 (58)
Acquired	451 (34)	49 (16)	95 (22)	307 (53)
Congenital	101 (8)	23 (7)	49 (11)	29 (5)
Neurological and motor disorder	298 (22)	71 (22)	129 (29)	98 (17)
Syndromic disorder[b]	226 (17)	60 (19)	66 (15)	100 (17)
Cognitive impairment	220 (16)	84 (27)	69 (16)	67 (12)
Liver disease	141 (11)	25 (8)	73 (17)	43 (7)
Skeletal disorder	82 (6)	36 (11)	25 (6)	21 (4)
Vision disorder	50 (4)	16 (5)	6 (1)	28 (5)
Pulmonary disease	48 (4)	14 (4)	21 (5)	13 (2)
Urogenital disorder	46 (3)	35 (11)	4 (1)	7 (1)
Immunological or haematological disorder	44 (3)	12 (4)	21 (5)	11 (2)
Intestinal disease	33 (3)	5 (2)	19 (4)	9 (2)
Malignancy	31 (2)	4 (1)	16 (4)	11 (2)
Endocrinological disorder	1 (0.07)	0 (0)	0 (0)	1 (0.2)
Preterm birth	4 (0.3)	0 (0)	3 (0.7)	1 (0.2)
Diabetes mellitus	8 (0.6)	0 (0)	2 (0.5)	6 (1.0)
Hearing disorder	17 (1.3)	2 (0.6)	6 (1.4)	9 (1.5)
Systemic disease	38 (2.8)	10 (3.2)	6 (1.4)	22 (3.8)
Unspecified	111 (8)	43 (14)	32 (7)	36 (6)

[a]Percentages sum to >100, as they are calculated per total of comorbid patients (not per number of comorbidities) and as one patient could have multiple comorbidities.
[b]including Turner syndrome (1), Patau syndrome (1), Down syndrome (2), DiGeorge syndrome (1), Prader–Willi syndrome (1), Frasier syndrome (1), Schimke syndrome (3), Wolf Hirschhorn syndrome (1), Williams syndrome (1), Klippel–Trenaunay syndrome (1), WAGR syndrome (1), Alagille syndrome (1), Pierson syndrome (1), Mainzer–Saldino syndrome (1), Nail–Patella syndrome (1), Star syndrome (1), Denys–Drash syndrome (1), Joubert syndrome (5), Cogan syndrome (2), Seckel syndrome (1), VACTERL (4), Noonan syndrome (1), Cornelia de Lange syndrome (1), Siamese twin (1), Toriello–Carey syndrome (1), Freeman–Sheldon syndrome (1), Marfan syndrome (2), Bardet–Biedl syndrome (5), Klippel–Feil syndrome (1), Silver–Russel syndrome (1), Mowat–Wilson syndrome (1), Goldenhar syndrome (1), Smith–Lemli–Optiz syndrome (1), renal coloboma syndrome (1), branchio-oto-renal syndrome (4), Ochoa syndrome (4), neurofibromatosis (3), polyglandular type 1 syndrome (1), Kallmann syndrome (1), Recklinghausen disease (1) and Goldman–Favre syndrome (1).

After adjustment for age, sex, primary kidney disease, country and income, 5-year access to KT was 33% lower for patients with comorbidities [adjusted hazard ratio (aHR) 0.67 (95% CI 0.61–0.74)]. Similarly, a greater number or more severe comorbidities were associated with a lower access to transplantation (Table 3).

Patient survival on KRT

In total, 277 patients died during the first 5 years on KRT. Five-year mortality was higher in the comorbidities group (10%) than in the group without comorbidities (7%; Fig. 3). The risk of death was significantly higher in patients with than without comorbidities [aHR 1.79 (95% CI 1.38–2.32)] and was even higher in case of three or more [aHR 3.32 (95% CI 1.98–5.58)] or severe comorbidities [aHR 2.86 (95% CI 1.98–4.13)] (Table 4). However, after KT there was no association between the presence, number or severity of comorbidities and mortality, whereas dialysis patients with comorbidities showed a significantly higher mortality risk compared with dialysis patients without any comorbidities. This association was even stronger in case of three or more [aHR 2.80 (95% CI 1.63–4.84)] or severe comorbidities [aHR 2.65 (95% CI 1.79–3.91)].

Kidney graft survival

Once transplanted, 92% ($n = 2125$) of the patients were still alive with a functioning graft 5 years after KT while 8% ($n = 193$) experienced graft failure during this time (Fig. 4). There was no association between the presence of comorbidities and the likelihood of experiencing graft failure. HRs for graft failure were not significantly different in case of the presence [aHR 1.18 (95% CI 0.84–1.65)], greater number [three or more; aHR 1.66 (95% CI 0.79–3.50)] and severity [aHR 1.39 (95% CI 0.82–2.38)] of comorbidities compared with patients without comorbidities (Supplementary Table S2). Moreover, the presence of comorbidities was not associated with death-censored graft failure.

Sensitivity analyses

After excluding patients with acquired cardiovascular diseases from the analyses, results were similar to the total cohort, with significantly lower access to KT [aHR 0.62 (95% CI 0.55–0.69)] and a higher mortality risk [aHR 1.88 (95% CI 1.43–2.48)] for patients with comorbidities compared with those without (Supplementary Table S3A–C).

Table 2: Patient characteristics according to the absence or presence of comorbidities.

Characteristics	Comorbidity		Total (N = 4127), n (%)	P-value for statistical difference[a]
	Absent [n = 2785 (68%)], n (%)	Present [n = 1342 (33%)], n (%)		
Sex				<.001
Female	1117 (40)	631 (47)	1748 (42)	
Male	1668 (60)	711 (53)	2379 (58)	
Age at KRT (years)				.16
0–<5	699 (25)	325 (24)	1024 (25)	.54
5–≤10	608 (22)	334 (25)	942 (23)	.03
10–≤15	993 (36)	450 (34)	1443 (35)	.18
≥15	485 (17)	233 (17)	718 (17)	.97
Age at KRT start (years), median (IQR)	10.5 (5.0–14.1)	10.2 (5.2–14.0)	10.4 (5.1–14.1)	.46
Primary kidney disease				<.001
CAKUT	993 (36)	400 (30)	1393 (34)	.002
Glomerulonephritis	520 (19)	236 (18)	756 (18)	.40
Cystic kidney disease	297 (11)	213 (16)	510 (12)	<.001
HUS	158 (6)	26 (2)	184 (5)	<.001
Hereditary nephropathy	105 (4)	73 (5)	178 (4)	.013
Metabolic disease	87 (3)	34 (3)	121 (3)	.29
Vasculitis	42 (2)	26 (2)	68 (2)	.31
Ischaemic kidney failure	19 (0.7)	31 (2)	50 (1)	<.001
Miscellaneous	335 (12)	191 (14)	526 (13)	.05
Unknown/missing	229 (8)	112 (8)	341 (8)	.89
Treatment modality at KRT start				<.001
HD	1024 (37)	539 (40)	1563 (38)	.04
PD	1228 (44)	641 (48)	1869 (45)	.03
Pre-emptive KT	509 (18)	158 (12)	667 (16)	<.001
Deceased donor	161 (32)	68 (43)	229 (34)	.008
Living donor	285 (56)	82 (51.9)	367 (55)	.37
Unknown donor	63 (12)	8 (5.1)	71 (11)	.009
Unknown/missing	24 (0.9)	4 (0.3)	28 (0.7)	.004
GDP				<.001
Low (<$12 665)	848 (31)	317 (24)	1165 (28)	<.001
Middle ($12 665–<$22 934)	1299 (47)	442 (33)	1741 (42)	<.001
High (≥$22 934)	638 (23)	583 (43)	1221 (30)	<.001

Percentages are sums over column for each category.
Abbreviations: KRT, kidney replacement therapy; IQR, interquartile range; CAKUT, congenital anomalies of the kidney and urinary tract; HUS, hemolytic uremic syndrome; HD, hemodialysis; PD, peritoneal dialysis; GDP, gross domestic product.
[a]Using Chi-square, except for median age (Kruskal-Wallis).

When considering only patients with reported comorbidity status, we found similar results compared with the main cohort. Similarly, after assuming at least one comorbidity for patients with missing information on comorbidity status, results did not differ from our main analyses (Supplementary Table S4A–C).

Furthermore, when analysing subgroups with neurological and motor disorders, cognitive problems and syndromic disorders, these patients had significantly lower access to KT, higher mortality and a similar graft survival compared with patients without any reported comorbidity (Supplementary Table S5A–C).

DISCUSSION

We found a high prevalence of comorbidities in European children starting KRT, with a steady increase over the past decade. Comorbidities are significantly less frequent in KRT patients from lower-income countries. Patients with comorbidities had a higher mortality on dialysis, while there was no such difference after KT. Paediatric patients with comorbidities had lower overall access to KT and a lower rate of living donation. This effect was most pronounced for patients with severe or multiple comorbidities and in lower-income countries. However, once transplanted, graft survival was similar in patients with and without comorbidities.

Prevalence of comorbidities

The prevalence of comorbidities in our study was comparable to that of a previous global registry study in children on PD [1] and was associated with country GDP. In fact, the proportion of patients presenting with non-renal comorbidities at KRT start was almost two times higher in high-income countries compared with low-income countries (43% in high-income versus 24% in low-income and 33% in middle-income countries). This might result from a lower access to KRT for children with comorbidities in these countries. It has been shown previously that provision of KRT in European children is associated with country GDP [20, 21]. Thus, in countries where KRT is a scarce resource, hurdles for children with pre-existing comorbidities could be disproportionately high. Moreover, although the effect described by Chesnaye

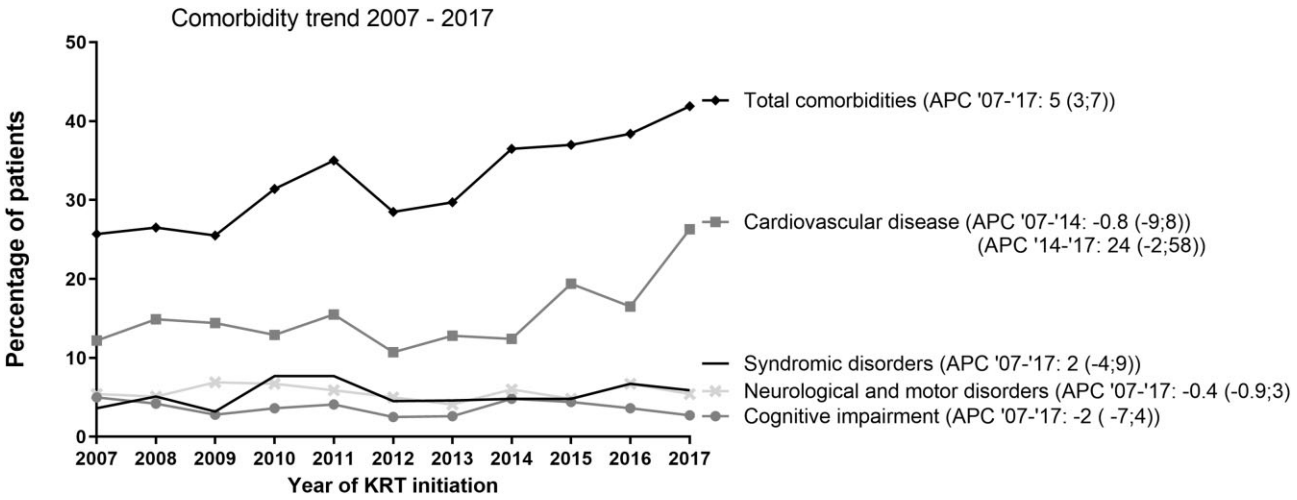


Figure 1: Comorbidity trend plot for Croatia, Czech Republic, Estonia, Greece, Portugal, Russia, Serbia, Slovakia, Slovenia, Spain and Switzerland.

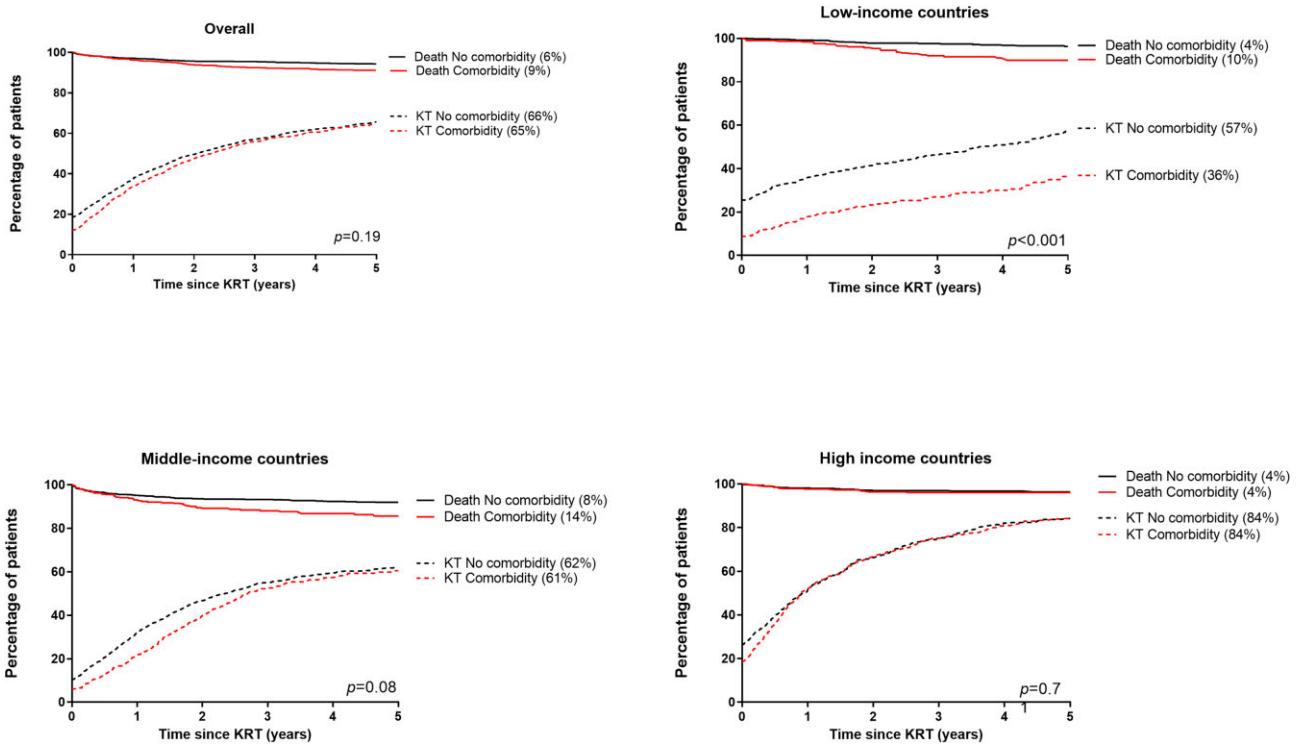


Figure 2: Cumulative incidence of receiving a KT adjusted for the competing event (death) in the first 5 years after initiating KRT stratified by income group.

et al. [20] was mainly explained by country macroeconomics, different ethical and religious considerations might also play a role.

To our knowledge, there are no data on the prevalence of comorbidities over time in children on KRT, and data in adults are not transferable due to the inherent differences in patient characteristics and comorbidities [3]. Here we have found an increase in the prevalence of comorbidities in children commencing KRT over the past decade. This might reflect an actual increase in the prevalence of multiple morbidities in CKD children due to improved survival through medical advances in neonatal and paediatric care, nursing and nutrition. On the other hand, it may be caused by an overall increase in the availability of paediatric KRT and therefore greater access to KRT for children with comorbidities promoted by improvements in the economic situation, as well as by physicians' change in mindset with respect to management of children with multiple organ disease. An increase in the incidence of paediatric KRT in Europe was seen for the period 1980–1990, but remained stable thereafter [22, 23]. Thus it seems plausible that improvements in medical care could have led to greater access to KRT for children with comorbidities while simultaneously some children are spared from KRT due to improvements in the management of CKD, leading to a steady incidence of KRT but a higher rate of comorbidities.

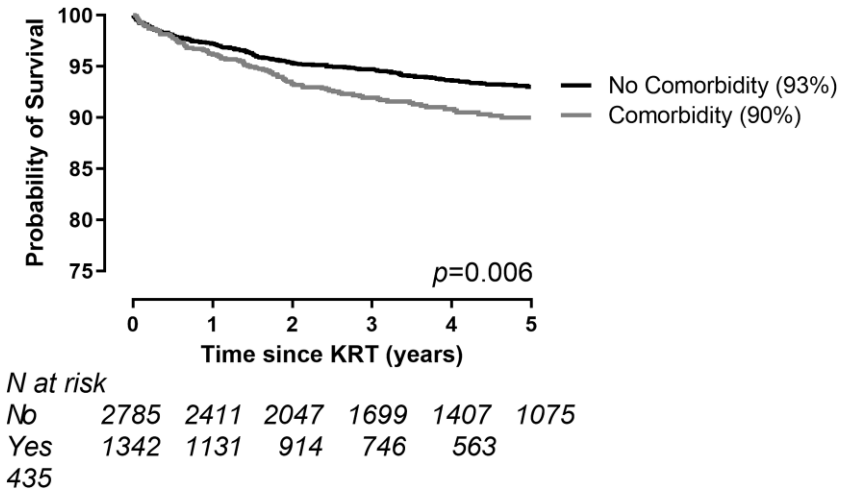


Figure 3: Kaplan–Meier patient survival on KRT by comorbidity status.

Table 3: HRs for access to KT 5 years after initiating KRT.

	Unadjusted		Adjusted[a]	
Variables	HR	95% CI	HR	95% CI
Comorbidity yes versus no	0.69	0.63–0.76	0.67	0.61–0.74
Comorbidities versus 0				
1	0.73	0.66–0.81	0.71	0.64–0.78
2	0.64	0.54–0.77	0.61	0.51–0.74
≥3	0.56	0.43–0.73	0.54	0.42–0.70
Severity of comorbidity versus no				
Mild	0.68	0.52–0.87	0.66	0.51–0.85
Ungraded	0.73	0.65–0.81	0.70	0.63–0.78
Severe	0.73	0.65–0.81	0.59	0.50–0.70

[a]Adjusted for age, sex, primary kidney disease, income and country.

Mortality

Similar to previous findings, we found a higher mortality risk in children with comorbidities on dialysis [1]. However, we did not observe excess mortality among KT patients. This could indicate that patients with comorbidities are more vulnerable to the detrimental effects of dialysis on mortality compared with those without comorbidities. On the other hand, this effect might be partly explained by selection since some patients with severe comorbidities might not have been deemed suitable transplant candidates and therefore remained on dialysis. Accordingly, in our cohort, the rate of severe comorbidities was slightly higher in patients who stayed on dialysis than in those who were transplanted (9% versus 7%).

Access to KT and association with mortality

Children on dialysis have a several-fold higher mortality risk compared with children after KT, particularly after pre-emptive transplantation [9–11]. We showed that children with comorbidities in Europe have a lower access to (pre-emptive) KT. The higher mortality risk observed in these children could therefore be partially explained by their lower access to KT. Consequently, children with comorbidities might benefit from earlier KT. However, it should be noted that the dialysis population had a higher rate of comorbidities in our cohort, likely due to selection of healthier patients for transplantation. Therefore, comorbidities should be considered as a confounder in future KRT outcome studies. A recent ESPN/ERA Registry study showed that country wealth has a major impact on access to KT, being responsible for 67% of the variation between countries [24]. Infrastructural and logistic reasons [25], political/governmental transplantation policies [26, 27] and other factors related to country macroeconomics might contribute to this. In our cohort, children with comorbidities from low-GDP countries had the lowest access to KT. Thus comorbid children from these countries seem to be more severely affected by restrictions to KT.

Outcome after KT

Our study suggests that the presence of comorbidities does not profoundly impair patient or graft survival after KT, even for those with severe or multiple comorbidities (Supplementary Table S2). This is a significant finding since the decision for KT in these patients is often difficult. Besides improved quality of life and reduced suffering, one of the key questions in each individual patient is whether survival will improve after KT [28–30]. Until the 1980s, severe mental retardation was considered a contraindication for transplantation, but more recent studies have shown a good outcome after KT in children with these conditions [31–33] and current guidelines recommend not to exclude candidates from KT because of non-progressive intellectual, developmental or cognitive disability.

Strengths and limitations

Our study has several limitations. Due to the observational nature, we cannot make definite statements on differential outcomes of treatment modalities. Individual decisions for KRT and KT are likely to be influenced by the presence of comorbidities, resulting in selection bias. Furthermore, some of the pre-existing comorbidities at KRT initiation can be interpreted as complications of CKD, namely frequent findings of hypertension and left ventricular hypertrophy. Since these conditions typically improve through KRT and KT, they might have a different influence on the physician's decision to initiate KRT or perform KT compared with comorbidities that are truly unrelated to CKD. Therefore, we performed a sensitivity analysis excluding patients with

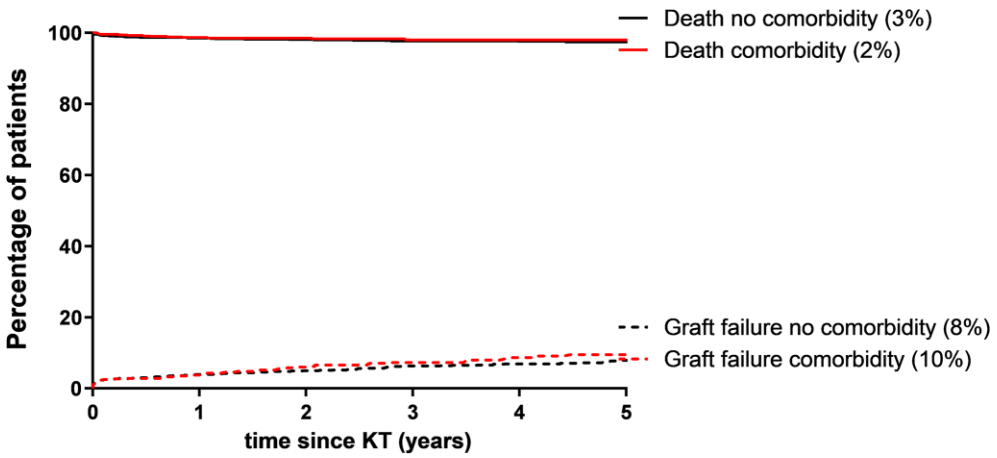


Figure 4: Cumulative incidence of graft failure after KT with subsequent need for dialysis and death by comorbidity status 5 years after KT.

Table 4: HRs for the association between comorbidity status and mortality on KRT.

	Unadjusted		Adjusted[a]	
Characteristics	HR	95% CI	HR	95% CI
Total population				
Comorbidity yes versus no	1.80	1.40–2.33	1.79	1.38–2.32
Comorbidities versus 0				
1	1.51	1.12–2.04	1.53	1.13–2.07
2	2.21	1.45–3.36	2.14	1.40–3.28
≥3	3.55	2.14–5.89	3.32	1.98–5.58
Severity of comorbidity versus no				
Mild	1.29	0.52–3.21	1.30	0.52–3.24
Ungraded	1.52	1.13–2.05	1.50	1.12–2.02
Severe	2.77	1.93–3.96	2.86	1.98–4.13
Dialysis population[b]				
Comorbidity yes versus no	1.67	1.27–2.21	1.60	1.21–2.13
Comorbidities versus 0				
1	1.40	1.01–1.94	1.39	1.00–1.94
2	2.02	1.28–3.17	1.82	1.15–2.88
≥3	3.14	1.85–5.32	2.80	1.63–4.84
Severity of comorbidity versus no				
Mild	1.38	0.55–3.43	1.39	0.55–3.49
Ungraded	1.37	0.98–1.90	1.29	0.92–1.80
Severe	2.63	1.80–3.84	2.65	1.79–3.91
Transplant population[c]				
Comorbidity yes versus no	1.04	0.50–2.14	1.41	0.67–2.93
Comorbidities versus 0				
1	0.94	0.41–2.13	1.23	0.54–2.82
2	1.45	0.43–4.95	2.40	0.68–8.48
≥3	1.06	0.14–8.15	1.47	0.19–11.42
Severity of comorbidity versus no				
Mild	–[d]		–[d]	
Ungraded	1.11	0.51–2.42	1.49	0.67–3.31
Severe	1.18	0.35–4.04	1.74	0.50–6.09

[a]Adjusted for age, sex, primary kidney disease, income and country.
[b]Patients were censored at KT.
[c]Follow-up since KT. Additional adjustment was made for donor type.
[d]Number of patients was too low to obtain an effect estimate.

acquired cardiovascular disease, showing similar results. Moreover, since the ESPN/ERA Registry is a multinational registry, reporting habits may differ between countries and time periods. However, we performed several sensitivity analyses to account for possible ambiguities in missing information on comorbidities. None of these analyses changed our results, indicating that there is no systematic reporting bias in the data.

CONCLUSION

Children on KRT in Europe seem to be increasingly affected by comorbidities. While these comorbidities impair survival, especially for children on dialysis, as well as their access to KT, outcomes after KT are not affected to the same extent. KT should be considered as early as possible in all children with comorbidities because of its impact not only on survival, but also on the quality of life of the patient and his/her family. Especially in low-income countries, improvements in kidney care might result in an increase in children initiating KRT with comorbidities in the future. Further studies should be undertaken to identify barriers to KT for children with comorbidities across Europe.

SUPPLEMENTRY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

R.S. and S.D. contributed equally to this work. R.S., S.D. and M.B. designed the study, revised and analysed data and wrote the manuscript. J.H., E.V., J.W.G. and K.J.J designed the study and reviewed and edited the manuscript. A.B., C.B., B.B., P.B., F.B., S.C., I.G., K.H., H.H., F.E.M.B., T.E.P., F.P., L.A.P., L.P., S.P., A.B., C.C., J.T., E.S., G.S., K.V. and J.O. contributed patient data and reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this manuscript cannot be shared with any third party because the national registries that provided data to the ESPN/ERA Registry remain the owners of the data.

CONFLICT OF INTEREST STATEMENT

None declared.

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