Mortality in Children Treated With Maintenance Peritoneal Dialysis: Findings From the International Pediatric Peritoneal Dialysis Network Registry

Sophie Ploos van Amstel, Marlies Noordzij, Dagmara Borzych-Duzalka, Nicholas C. Chesnaye, Hong Xu, Lesley Rees, Il-Soo Ha, Zenaida L. Antonio, Nakysa Hooman, William Wong, Karel Vondrak, Yok Chin Yap, Hiren Patel, Maria Szczepanska, Sara Testa, Monica Galanti, Jameela A. Kari, Charlotte Samaille, Sevcan A. Bakkaloglu, Wai-Ming Lai, Luisa Fernanda Rojas, Mabel Sandoval Diaz, Biswanath Basu, Alicia Neu, Bradley A. Warady, Kitty J. Jager, and Franz Schaefer

Rationale & Objective: Research on pediatric kidney replacement therapy (KRT) has primarily focused on Europe and North America. In this study, we describe the mortality risk of children treated with maintenance peritoneal dialysis (MPD) in different parts of the world and characterize the associated demographic and macroeconomic factors.

Study Design: Prospective cohort study.

Setting & Participants: Patients younger than 19 years at inclusion into the International Pediatric Peritoneal Dialysis Network registry, who initiated MPD between 1996 and 2017.

Exposure: Region as primary exposure (Asia, Western Europe, Eastern Europe, Latin America, North America, and Oceania). Other demographic, clinical, and macroeconomic (4 income groups based on gross national income) factors also were studied.

Outcome: All-cause MPD mortality.

Analytical Approach: Patients were observed for 3 years, and the mortality rates in different regions and income groups were calculated. Cause-specific hazards models with random effects were fit to calculate the proportional change in variance for factors that could explain variation in mortality rates.

Results: A total of 2,956 patients with a median age of 7.8 years at the start of KRT were included. After 3 years, the overall probability of death was 5%, ranging from 2% in North America to 9% in Eastern Europe. Mortality rates were higher in low-income countries than in high-income countries. Income category explained 50.1% of the variance in mortality risk between regions. Other explanatory factors included peritoneal dialysis modality at start (22.5%) and body mass index (11.1%).

Limitations: The interpretation of interregional survival differences as found in this study may be hampered by selection bias.

Conclusions: This study shows that the overall 3-year patient survival on pediatric MPD is high, and that country income is associated with patient survival.

Maintenance peritoneal dialysis (MPD) is a well-established treatment option for children with kidney failure.[1] Usually performed at home by the adult caregivers, MPD is the preferred dialysis modality in children due to its applicability across the entire pediatric age range and compatibility with schooling and social life. Notwithstanding its successful implementation in the pediatric population, MPD remains a challenging therapy subject to significant patient morbidity and mortality.[2,3]

Population-based registries in Europe and North America have provided information on patient survival among children undergoing dialysis and kidney transplantation.[4,5] Although the survival rates appear to have improved over the past 3 decades, annual mortality rates for children on dialysis are at least 30 times higher than those of the general pediatric population, with 5-year patient survival around 84% and 90% in North American and European children, respectively.[3,4]

Young patient age, late referral to a pediatric nephrologist, glomerular disease, the presence of comorbidities, low socioeconomic status, and reduced access to kidney transplantation have been identified as potential mortality risk factors for children undergoing maintenance dialysis.[3,6-10] In addition, macroeconomic factors appear to play a crucial role in the survival of children on kidney replacement therapy (KRT). A recent comparison of children's mortality rates across 32 European countries revealed an inverse association between country-specific mortality rates and the gross domestic product per capita.[11]

While epidemiological research into pediatric KRT has largely focused on Europe and North America, the majority (62.5%) of children undergoing maintenance dialysis live in other parts of the globe.[12] As the variation in environmental, ethnic, cultural, political, and macroeconomic factors is larger on the global scale, this may impact patient survival through the timing of KRT initiation, the criteria of patient selection for KRT, the choice of dialysis modality, dialysis treatment quality and treatment times, and the prevalence of non–dialysis-related risk factors.

PLAIN-LANGUAGE SUMMARY

So far, research on children who are treated with dialysis or have received a kidney transplant has focused on Europe and North America. In this study, we describe the mortality risk of children on maintenance peritoneal dialysis in different parts of the world and assess which factors are associated with patient survival. We included 2,956 patients younger than 19 years from the International Pediatric Peritoneal Dialysis Network who started maintenance peritoneal dialysis between 1996 and 2017. After 3 years, the overall probability of death was 5%, ranging from 2% in North America to 9% in Eastern Europe. Mortality was higher in low-income countries than in high-income countries. This study shows that the overall patient survival on maintenance peritoneal dialysis is high in children, and that country income is associated with patient survival.

For more than a decade, the International Pediatric Peritoneal Dialysis Network (IPPN) Registry has been collecting patient outcome data along with comprehensive clinical, biochemical, and treatment information from a large number of children undergoing MPD around the globe.[13] Earlier research based on this database identified associations of patient survival with clinical and laboratory findings[10,14] and with macroeconomic factors.[15] In the current study, we used IPPN data to describe (1) the current global and regional mortality risk of children treated with MPD, (2) the main causes of death, and (3) the macroeconomic factors that are associated with mortality risk and/or the distribution of death causes around the globe.

Methods

Study Population

The IPPN Registry collects prospective data from pediatric peritoneal dialysis (PD) centers worldwide. The participating centers are asked to enroll all their incident and prevalent MPD patients and to enter their data every 6 months until MPD is stopped. Data input to the IPPN Registry is voluntary and performed exclusively via an internet-based platform. Data entries are automatically checked for plausibility and completeness, and data protection is ensured by pseudonymized data input.

For the current study, we included all patients who were younger than 19 years at inclusion in the IPPN Registry and who started treatment with MPD between 1996 and 2017. The IPPN Registry's protocol was approved by the ethics committees/institutional review boards as required at each participating center. Written parental consent and, whenever appropriate, assent from patients was obtained.

Data Collection and Definitions

For the current study, the primary exposure of interest was region. We therefore divided the study cohort into regions based on the location of the center: Asia, Europe, Latin America, North America, and Oceania. An overview of the countries per region participating in the IPPN Registry is provided in Table S1. Because previous studies showed that there is a large variation within Europe, we subdivided Europe into Eastern and Western Europe.[11]

The economic wealth of each participating country was classified by the per-capita gross national income (GNI) in 2016 based on purchasing power parity converted to international dollars, using the tables published by the World Bank. An international dollar has the same purchasing power over GNI as a US dollar has in the United States. The majority of the countries contributing data to the IPPN Registry would be considered "high-income" countries according to the official criteria of the World Bank (GNI > $12,276).[16] To differentiate group effects associated with relative economic wealth in the present analysis, we readjusted the partition values, dividing countries into 4 income groups based on the GNI distribution within the IPPN cohort: low-income (<$12,000), lower-middle income ($12,000 to <$16,000), upper-middle income ($16,000 to <$45,000), and high-income ($45,000 or more).

For each patient, we extracted data on date of birth, sex, time on KRT before current episode of MPD, primary kidney disorder, the presence of comorbidities at the start of the current treatment, and events including death and cause of death, changes in treatment modality, and other reasons for discontinuation of MPD (ie, recovery of native kidney function or loss to follow-up assessment).

The presence of the following comorbidities was recorded: cognitive dysfunction, motor dysfunction, ocular dysfunction, hearing dysfunction, cardiac abnormality, pulmonary abnormality, osseous abnormality, or other abnormality. Primary kidney disorders were grouped into 5 categories: (1) congenital anomalies of the kidney and urinary tract (CAKUT) and other ciliopathies, (2) glomerulopathies, (3) chronic kidney disease after acute kidney injury, (4) metabolic disease, and (5) other/miscellaneous disease. Age at the start of MPD was grouped into 4 age categories: 0-4, 5-9, 10-14, and 15-19 years. Body mass index (BMI) z-scores at entry in the registry were calculated using WHO Child Growth Standards for children up to 2 years and CDC 2000 charts for children aged 2 to 20 years and grouped into 3 categories: underweight (<5th percentile), normal weight (5th–85th percentile), and overweight (>85th percentile).[17] Causes of death were classified as infection, malignancy, pulmonary edema, congestive heart failure, recurrence of disease, noninfectious dialysis-related complications, and other/miscellaneous disease. These causes were grouped into 4 categories: infection related, dialysis related, cardiovascular related (including pulmonary edema), and other death causes.

Statistical Analyses

Patient characteristics at inclusion in the IPPN Registry were expressed as median values with interquartile range for all numerical variables and as proportions for all categorical variables. Differences between regions in numerical variables were assessed using Kruskal-Wallis tests and differences in proportions using χ^2 tests.

The primary outcome studied was all-cause mortality on MPD, expressed as crude and adjusted (for age and sex) mortality rates per 100 patient-years; the primary exposures studied were region and GNI. Death cause–, region-, and GNI-specific mortality rates were also calculated. Differences in mortality rates between groups were tested using generalized linear models with a Poisson distribution (SAS Proc Genmod, dist=Poisson). These models also yielded the 95% confidence intervals around the rates.

To describe the probabilities pertaining to survival and modality switches in the overall population and per region, the cumulative incidence competing risks (CICR) method is preferred because it accounts for the effect of competing events.[18] A competing event is defined as an event that either hinders the observation of the event of interest or modifies the chance that this event occurs. We were interested in death on MPD, so switching to a different treatment modality (ie, hemodialysis [HD] or kidney transplantation) was considered a competing event. Patients were observed from the start of MPD until death, until switching to another treatment modality, or to the end of 3 years, whichever came first. For the sake of comparison with previous literature, we also included a Kaplan-Meier analysis.

Because variation in mortality rates could be attributed both to country-specific factors and to differences in patient characteristics, we used a cause-specific hazards model with random effects in which the baseline risk of mortality of a region is modeled as the random effect, and the effect of macroeconomic or patient factors is allowed to vary by region. The random effect for each region represents the degree of deviation in mortality risk from the overall mortality risk. The heterogeneity in mortality risk is reflected by the variance estimate of the random effect. The variance estimate in the baseline model represents the variation in mortality risk per region. Adding an explanatory factor to the model, on either country or patient level, allows the variance estimate to be adjusted for this factor. The proportional change in variance (PCV) after addition of this explanatory factor to the baseline model therefore allows examination of its effect on the variation in mortality risk between regions. The PCV is calculated by subtracting the adjusted variance from the baseline variance and dividing by the baseline variance. Negative values for PCV are explanatory for the variance (ie, the variance between regions is reduced) whereas positive values indicate an increase in variance.[11,19]

Covariates were only included in the multivariable models if they satisfied all 3 criteria for confounding. To be a potential confounder, a variable (1) must be a risk factor for the outcome (death), (2) must be associated with the exposure, and (3) must not be an effect of the exposure; this means that the variable should not be in the causal pathway.[20] For the primary exposure (region), no confounders could be identified, as is illustrated in the directed acyclic graph in Figure S1. Next, we created separate multivariate models to assess the associations of GNI, age, sex, primary kidney disorder, BMI, number of comorbidities, modality choice, and KRT vintage (in months) with all-cause mortality on MPD. Again, only those variables that fulfilled the criteria for confounding were included in those models.

Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). P < 0.05 was considered statistically significant.

Results

Cohort Characteristics

A total of 2,956 patients were included. Table 1 displays the variation in annual GNI in US dollars per capita and patient characteristics between regions. Most Asian countries (56.4%) fell in the lowest GNI quartile whereas Latin American countries tended to have a slightly higher GNI. In Western Europe, all countries fell in the higher GNI quartiles whereas Eastern European countries clustered within the middle quartiles. In North America all countries were classified as having a high GNI.

The median age at initiation of KRT was 7.8 years and varied between 4.9 years in Western Europe and 9.3 years in Asia. The median age at inclusion in the IPPN was 8.3 years, ranging from 5.3 in Western Europe to 9.8 in North America. In general, patients treated in Europe were younger than in Asia and North America (P < 0.001).

The most frequent primary kidney disorder was CAKUT and other ciliopathies (46.2%) followed by glomerulopathies (27.6%). North America and Eastern Europe had higher percentages of patients with a defined syndrome (17.7% and 17.6%, respectively) compared with other regions. Confirmed genetic disorders were significantly less common in Latin America (4.1% vs 12.4% overall). The most frequent comorbidities were cardiac abnormalities (14.1%), cognitive dysfunction (13.8%), and motor dysfunction (11.7%), with markedly higher percentages of all comorbidities except for hearing dysfunction reported in North America (P < 0.001).

Approximately one-third of the patients had received KRT before starting their current MPD treatment, of whom 20.1% had received a transplant and 79.9% had undergone dialysis treatment (HD, previous PD, or both). The time on KRT before inclusion in the IPPN Registry

Table 1. Patient Characteristics at Inclusion in the IPPN Registry

Characteristics	Total Cohort (N = 2,956)	Asia (n = 596)	Western Europe (n = 671)	Eastern Europe (n = 667)	Latin America (n = 584)	North America (n = 389)	Oceania (n = 49)	P
Macroeconomics								
Income class[a]								<0.001
<$12,000	25.4%	56.4%	0%	6.4%	33.2%	0%	0%	
$12,000-15,829	28.5%	31.5%	0%	64.3%	58.9%	0%	0%	
$15,830-45,790	21.1%	7.5%	55.0%	29.3%	7.9%	0%	92.5%	
>$45,790	25.0%	4.6%	45.0%	0%	0%	100%	7.5%	
GNI, ×$1,000[b]	14.3 [12.0-45.8]	12.0 [8.0-12.0]	43.7 [40.7-45.8]	13.3 [9.5-18.3]	12.3 [9.9-14.3]	56.3 [56.3-56.3]	40.3 [40.3-40.3]	<0.001
Patient Characteristics								
Male sex	55.8%	56.3%	59.5%	55.3%	53.8%	54.9%	46.9%	
Age at initiation of KRT, years	7.8 [1.9-12.8]	9.3 [5.2-12.9]	4.9 [0.7-11.8]	7.2 [1.8-12.7]	8.8 [3.4-12.7]	8.8 [1.0-14.1]	6.4 [1.5-11.1]	<0.001
Age at inclusion, years	8.3 [2.2-13.1]	9.5 [5.2-13.0]	5.3 [0.8-12.5]	7.6 [1.9-12.9]	9.3 [3.7-13.1]	9.8 [1.3-14.6]	7.0 [1.6-11.9]	<0.001
Age at inclusion								<0.001
0-4 years	35.5%	28.4%	48.1%	39.2%	29.7%	36.5%	38.8%	
5-9 years	22.5%	37.7%	18.2%	21.5%	24.9%	13.9%	26.5%	
10-14 years	28.7%	31.5%	20.0%	23.5%	37.9%	27.7%	30.6%	
15-19 years	13.2%	12.4%	13.7%	15.8%	7.5%	22.4%	4.1%	
Primary Kidney Disorder								
Category								<0.001
CAKUT and ciliopathies	46.2%	34.4%	49.0%	46.9%	51.2%	39.2%	36.7%	
Glomerulopathies	27.6%	36.6%	27.1%	28.0%	22.6%	28.5%	30.6%	
Post-AKI CKD	6.6%	4.5%	8.8%	8.7%	7.2%	5.6%	8.2%	
Metabolic diseases	1.8%	0.8%	2.1%	1.9%	1.2%	0.3%	2.0%	
Other	17.9%	23.3%	13.0%	14.5%	17.8%	26.4%	22.4%	
Defined syndrome	12.4%	8.8%	15.8%	17.6%	7.9%	17.7%	6.1%	<0.001
Confirmed genetic disorder	14.2%	13.9%	23.5%	15.4%	4.1%	12.6%	14.3%	<0.001
Comorbidities								
Cardiac abnormality	14.1%	13.7%	15.5%	14.1%	10.8%	24.9%	16.3%	<0.001
Cognitive dysfunction	13.8%	8.0%	19.5%	14.4%	11.6%	16.2%	12.2%	<0.001
Motor dysfunction	11.7%	5.0%	15.9%	12.9%	10.1%	16.2%	10.2%	<0.0001
Osseous abnormality	11.3%	8.0%	9.7%	16.7%	9.8%	20.8%	4.1%	<0.0001
Ocular dysfunction	9.8%	5.7%	14.8%	8.7%	5.3%	12.1%	8.2%	<0.001
Pulmonary abnormality	5.3%	2.9%	9.8%	4.5%	1.7%	11.3%	2.0%	<0.001
Hearing dysfunction	4.4%	2.6%	5.2%	4.8%	4.1%	5.9%	6.1%	0.1
Other abnormality	16.8%	13.3%	16.2%	26.7%	12.0%	27.9%	8.2%	<0.001

(Continued)

Table 1 (Cont'd). Patient Characteristics at Inclusion in the IPPN Registry

Characteristics	Total Cohort (N = 2,956)	Asia (n = 596)	Western Europe (n = 671)	Eastern Europe (n = 667)	Latin America (n = 584)	North America (n = 389)	Oceania (n = 49)	P
Treatment at Registry Entry								
Residual diuresis (mL/m² BSA)	400 [50-1,000]	300 [50-700]	300 [10-800]	600 [100–1,200]	614 [200-1,200]	0 [0-500]	400 [45-645]	<0.001
KRT vintage, months	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.0 [0.0-1.0]	0.0 [0.0-3.0]	0.0 [0.0-0.0]	<0.001
Dialysis before inclusion[c]	26.2%	31.4%	20.7%	21.2%	25.9%	39.1%	16.3%	0.05
Tx before inclusion	6.6%	2.9%	7.7%	5.8%	8.0%	10.8%	8.2%	<0.001
PD Modality at Registry Entry								
CAPD	23.5%	24.7%	11.5%	20.9%	35.6%	2.6%	2.0%	<0.001
APD	75.7%	74.6%	87.3%	76.9%	64.4%	97.4%	95.9%	
Other	0.6%	0.3%	1.0%	1.3%	0.0%	0.0%	2.0%	

Values for continuous variables given as median [interquartile range]. Abbreviations: AKI, acute kidney injury; APD, automated peritoneal dialysis; BSA, body surface area; CAKUT, congenital abnormalities of the kidney and urinary tract; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; GNI, gross national income; HD, hemodialysis; IPPN, International Pediatric Peritoneal Dialysis Network; KRT, kidney replacement therapy; PD, peritoneal dialysis; Tx, transplantation.
[a]Percentage of countries, US$ per capita.
[b]US$ per capita, Atlas method.
[c]HD and/or PD.

was very short (median 3.0 [interquartile range, 1.0–22.0] months). Upon entry to the registry, the majority were treated with automated PD (75.7%), followed by continuous ambulatory PD (23.5%), and other PD treatment (1.6%). The distribution of PD modalities differed significantly among regions (P < 0.001). The percentage of automated PD patients was highest in North America (95.1%).

Patient Survival

Because of the limited number of patients (n = 49), Oceania was excluded from the survival analyses. The median follow-up duration in the IPPN Registry was 1.68 [IQR, 0.8-3.0] years. MPD was stopped during the follow-up period in 1,969 patients, of whom 177 (9%) died. Other common causes for the follow-up period to end were kidney transplantation (64.6%), switch to HD (for several reasons, 9.1%), and loss to follow-up assessment (6.5%).

All-cause MPD mortality rates per 100 patient-years per region are displayed in Figure 1. The mortality rate in North America was significantly lower than the mortality rates in other regions. Mortality rates adjusted for region were highest in low-income countries, followed by the lower-middle-income countries (Fig 1).

When stratifying mortality rates according to region and cause of death, infection-related death was highest in low-income countries, and particularly in Eastern Europe and Latin America (Fig 2). Cardiovascular-related death declined with increasing GNI. Similarly, death due to dialysis-related complications was highest in the lower GNI classes, but was also slightly elevated in the highest income group.

The CICR analysis (Fig 3A) shows that after 3 years, the probability of death in the overall cohort was 5%. The probability of switching to HD as a result of technique failure was 6%. Almost half of the children received a kidney allograft (43%), and the remaining 46% were still alive on MPD. When we repeated this analysis including only the patients incident on MPD, this did not change our findings. Figure 3B-F displays the region-specific CICR probabilities, with the lowest probability of death in North America (2%) and the highest in Eastern Europe (9%).

CICR analysis was also performed by GNI quartile (Fig 4). It showed that after 3 years of follow-up assessment patients in countries with a low GNI tended to have a higher mortality risk and a lower probability of receiving a kidney transplant.

Because there was substantial variation in patient survival by region, we used cause-specific hazards models with random effects to assess whether the differences in other factors could explain this variation. We built separate statistical models for these factors, which are specified in Table 2. Also the PCV per factor is displayed in Table 2. Country differences in GNI explained 50.1%, choice of modality explained 22.5%, and BMI explained 11.1% of
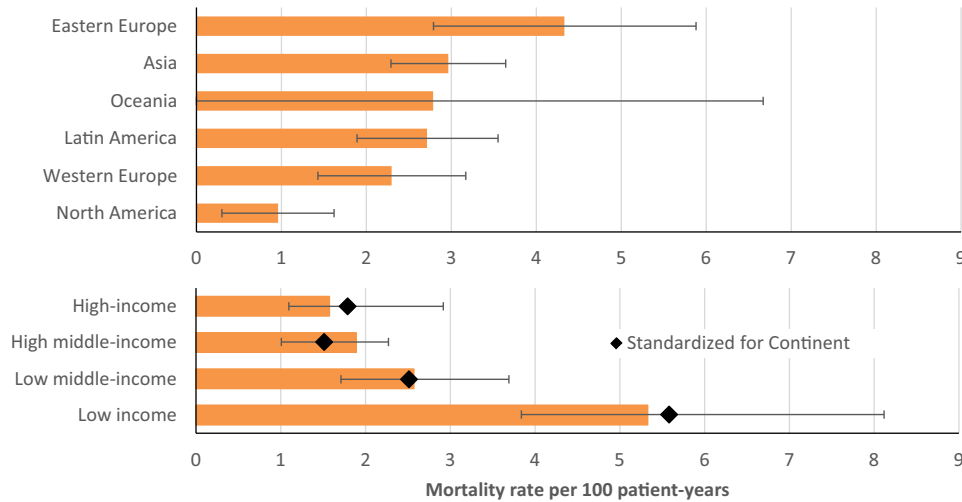
Figure 1. All-cause maintenance peritoneal dialysis (MPD) mortality rates per 100 patient-years with 95% confidence intervals per region and per gross national income (GNI) category. GNI category based on data from the World Bank.

the variance among regions. Other minor explanatory factors included KRT vintage (9.3%) and sex (2.4%). Primary kidney disorder, age group, and number of comorbidities only increased the variance between regions (2.1%, 32.7%, and 67.7%, respectively), meaning that if the distribution of these factors had been the same across regions the interregional survival differences would have been even larger.
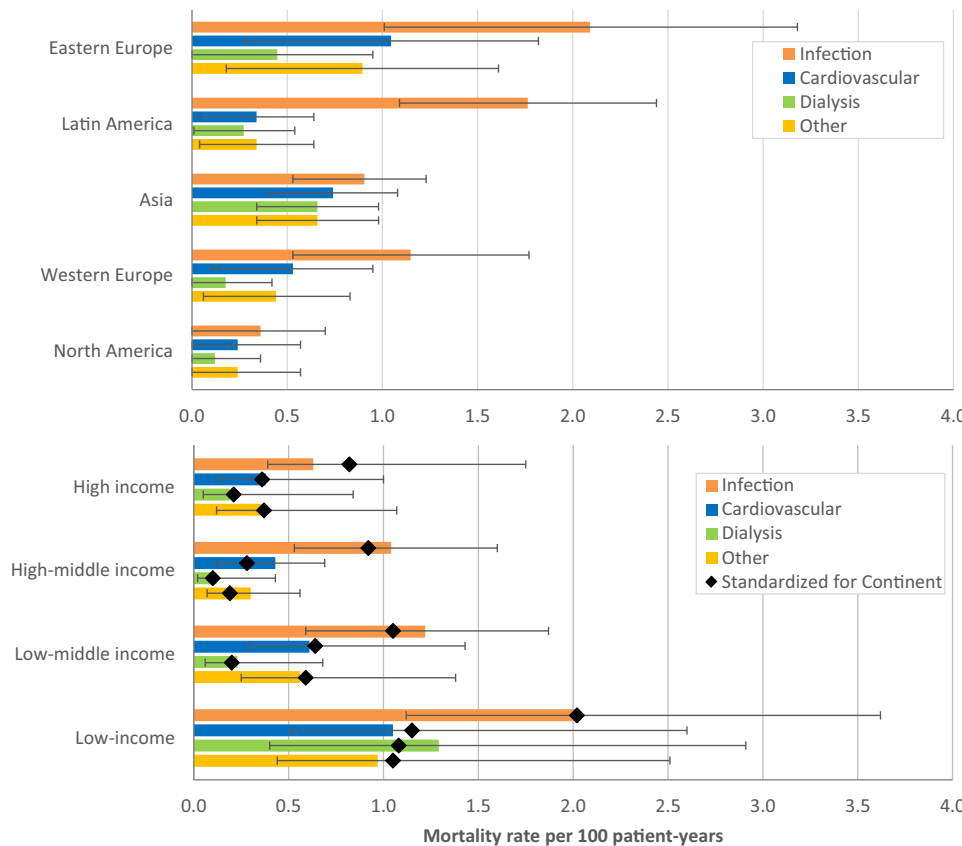
Figure 2. Death-cause specific mortality rates per 100 patient years per region and per gross national income category.
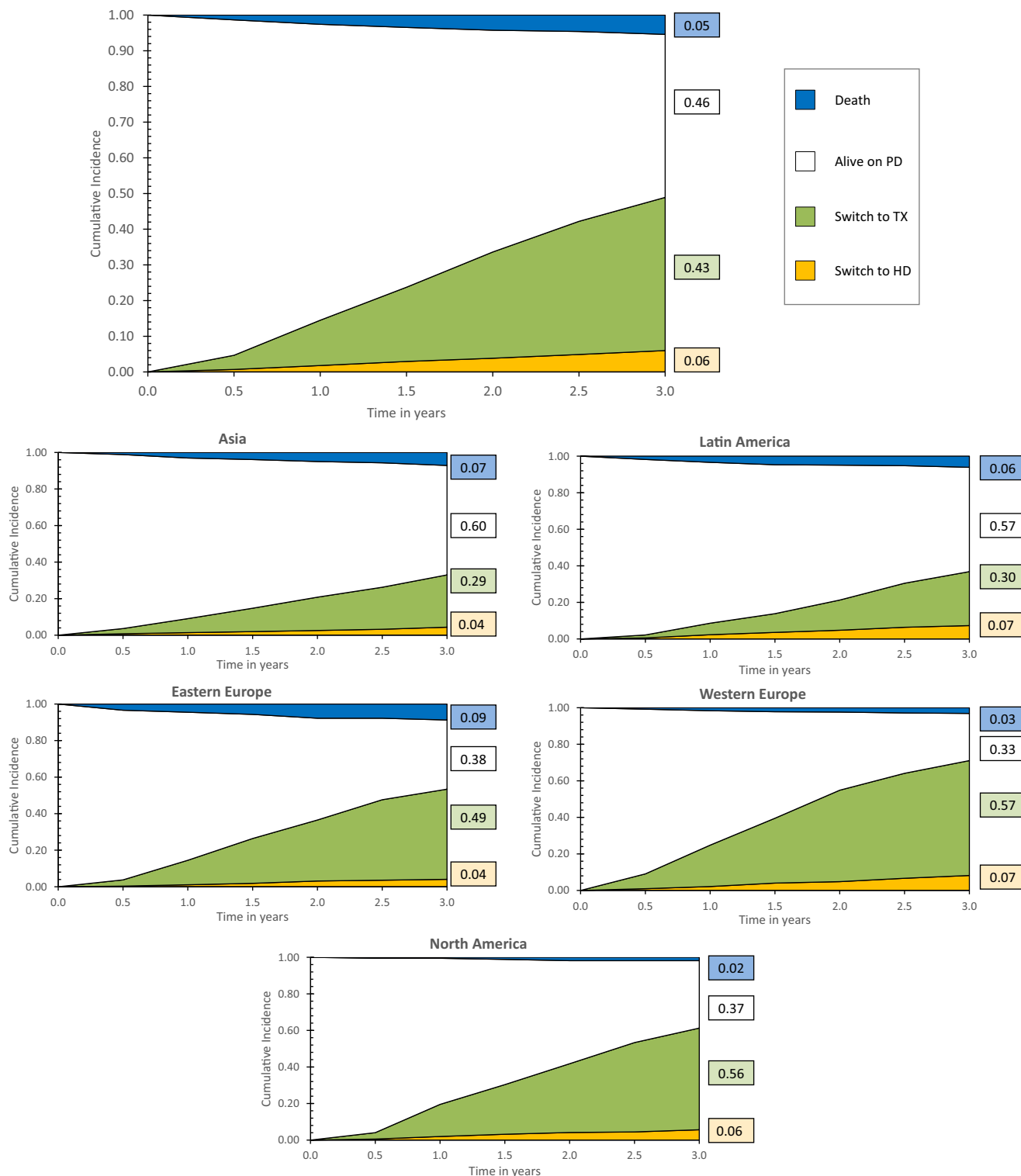
Figure 3. Probability of death, switch to hemodialysis, or receiving a transplant in the total International Pediatric Peritoneal Dialysis Network cohort per region during 3 years of follow-up assessment. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; TX, transplantation.

Discussion

In this study, which was based on a large, worldwide cohort of children on MPD, the CICR analysis showed a global probability of death on MPD of 5% within 3 years of follow-up assessment. However, substantial interregional variation exists in patient survival on MPD, as well as in the causes of death. Our analysis showed that, in
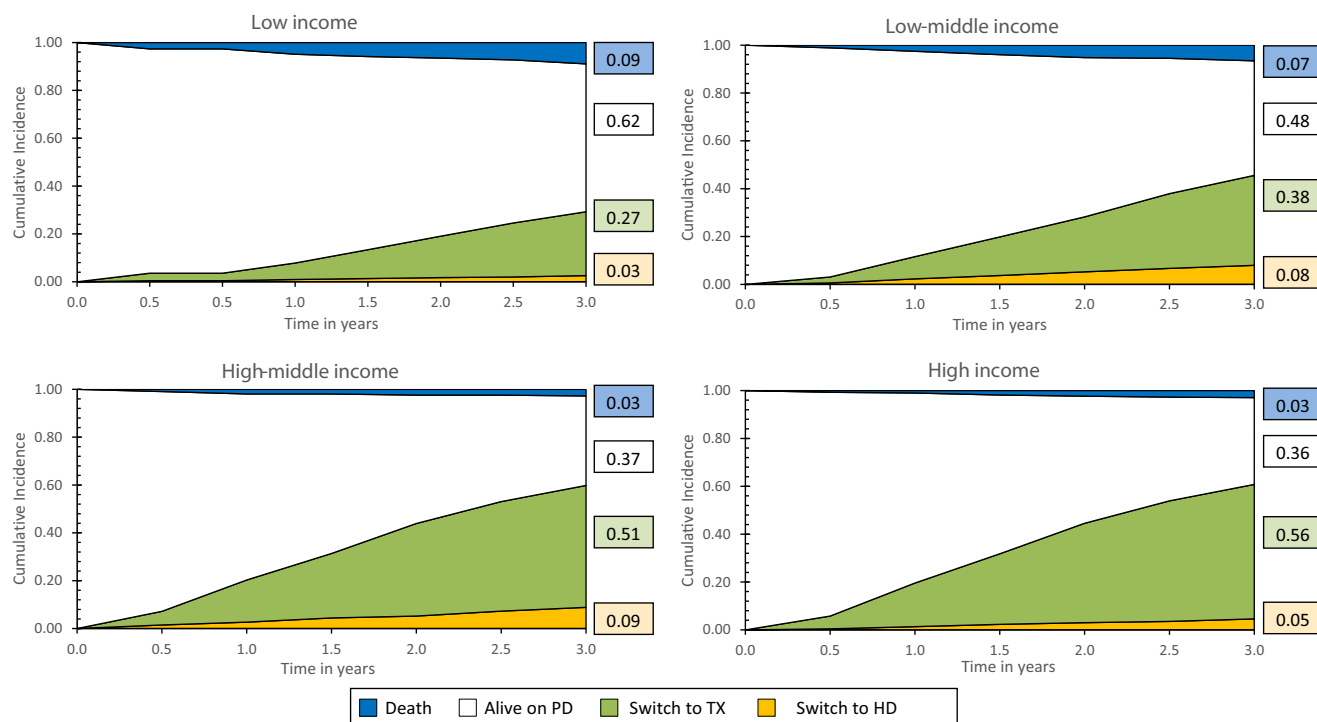
Figure 4. Probability of death, switch to hemodialysis, or receiving a transplant per income category during 3 years of follow-up assessment. Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; TX, transplantation.

decreasing order, GNI, choice of modality at start, and BMI may explain these interregional differences.

Research based on an earlier cohort of the IPPN Registry already showed that global economic disparities influence practices and outcomes of MPD in children.[15] In this study, patient survival on MPD was significantly higher in patients from countries with a GNI exceeding $28,000 (94.1% at 5 years) compared with countries with a GNI of less than $28,000 (88.7%). In line with our findings, Chesnaye et al[11] showed that there is considerable variation in mortality rates in children treated with KRT within Europe, and that macroeconomic factors affected pediatric KRT survival, even within the developed part of Europe with the median GNI exceeding $10,000. Intraregional distribution differences in GNI and mortality risk as seen in Europe may also play a role in other regions, especially in Asia. Countries such as Singapore and Hong Kong differ substantially from, for example, India and Pakistan, particularly with regard to wealth and health expenditure.[16,17] Therefore we also divided our cohort based on national income in addition to geographical location. Competing risk analyses in these GNI subgroups showed that lower income is associated with a higher mortality risk, a higher risk of switching to HD, and a lower probability of receiving a kidney transplant.

Although differences in macroeconomics seem to be largely responsible for the variance between regions, we found that other factors, independent from GNI, may also influence pediatric MPD survival.

The causes of death also varied between regions. We found that non–dialysis-related infection was the most common cause of death in all regions, with the highest mortality found in Latin America and Eastern Europe. This may be explained by the significantly higher burden of communicable diseases in these regions, as was demonstrated by the Global Burden of Disease study.[21] The latter study showed that in countries with a lower GNI, deaths due to communicable, maternal, neonatal, and nutritional disease occurred more often. The number of deaths due to these causes has sharply decreased over the past decades but remains high in low-income compared with high-income countries. Another important cause of death was cardiovascular disease. The mortality rate due to cardiovascular-related death decreased with increasing GNI. This might be due to the fact that in wealthier countries more cardiovascular complications are prevented by an increased use of antihypertensive drugs and closer surveillance of other cardiovascular risk factors.[22,23]

The main strength of this study is the inclusion of MPD patients from across the globe, which enabled for the first time a study of the effect of macroeconomic indicators on survival in children on MPD. In addition, the dataset contained comprehensive and complete clinical data of these patients.

A limitation of our study is that online registries such as the IPPN may suffer from problems with the accuracy and quality of the data, but several data checks are

Table 2. Variance and Proportional Change in Variance

Exposure	Confounders	Variance (SE)	PCV
Baseline model			
Region	—	0.24 (0.20)	Reference
Macroeconomics			
GNI	None	0.12 (0.13)	−50.1%
Patient factors			
Age	GNI, sex	0.31 (0.26)	+32.7%
Sex	GNI, age	0.23 (0.20)	−2.4%
Primary kidney disorder	GNI, sex, age	0.24 (0.21)	+2.1%
BMI	GNI, sex, age, primary kidney disorder, modality, KRT vintage	0.21 (0.18)	−11.1%
Comorbidities	GNI, sex, age, primary kidney disorder, modality, KRT vintage, BMI	0.40 (0.32)	+67.7%
Treatment factors			
Choice of modality	GNI, age, sex, primary kidney disorder	0.18 (0.17)	−22.5%
KRT vintage	GNI, age, sex, primary kidney disorder, modality	0.21 (0.19)	−9.3%

For all exposures separate statistical models were built, including those covariates that fulfill the 3 criteria for confounding (see Methods). Abbreviations: BMI, body mass index; GNI, gross national income; KRT, kidney replacement therapy; PCV, proportional change in variance.

applied to minimize the influence of these issues. Another limitation is that selection bias may have had an influence on our findings. It is generally assumed that survival on MPD is lower in the developing world, although recent mortality reports are lacking.[16,24–26] Our Kaplan-Meier analysis showed that 3-year overall patient survival on MPD in the IPPN cohort was 93%. This overall survival, including patients from both developed and developing countries, was similar to the 92% survival found by the US Renal Data System (USRDS), a population-based kidney disease registry in the United States that used a rather similar analysis approach, although there were some subtle differences (ie, no censoring at switch to HD).[4] This suggests at least some degree of selection bias in the IPPN sample, possibly due to a higher participation of specialized MPD centers across the world, which may focus more on MPD patients and adhere better to guidelines. We should, however, keep in mind that the Kaplan-Meier estimates were only included in the current study for the sake of comparison and are somewhat biased due to the presence of competing risks.

Comparison of survival as reported in population-based registries per region shows that survival in the North American patients in the IPPN cohort is better than survival in the USRDS: 97% in IPPN versus 92% in USRDS. This could in part be due to the inclusion of patients aged 18 years in the IPPN, who are excluded in USRDS. It could also suggest that selection bias was slightly more pronounced in patients from North America. This may explain the marginal survival difference between North America and Western Europe in the current study. From Western Europe a much larger sample was included in the IPPN, suggesting a greater coverage and thus a better representative sample compared with North America. In line with this notion, survival in the IPPN Registry was almost identical to the survival rates observed in the population-based European Society of Paediatric Nephrology/European Renal Association–European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry (95% in IPPN vs 94% in the ESPN/ERA-EDTA Registry using the same age and sex distribution [M. Bonthuis, personal communication, June 2020]). Selection bias also seemed to play a role in the poor survival found in Eastern European patients, as the survival in the IPPN was lower than that reported in the ESPN/ERA-EDTA Registry (89% vs 92% [M. Bonthuis, personal communication, June 2020]). We cannot explain this, although center selection and random variation may play a role. Taken together, this suggests that our estimation of MPD patient survival is skewed in both positive and negative directions. As a consequence, the association between macroeconomics and MPD survival as we found in this IPPN cohort may have been diluted, and possibly the true association of macroeconomics and MPD survival at the population level may be stronger.

For the purpose of interregional outcome comparisons, population-based studies, such as the recently launched International Pediatric Nephrology Association Global Renal Replacement Therapy (IPNA Global RRT) Registry, are more suitable, provided that contributing registries have a sufficiently high coverage of patients in their countries. The IPNA Registry aims to combine all existing pediatric national renal registries and provide a platform for countries that do not have such a registry yet.

In conclusion, this study shows that the overall 3-year patient survival on pediatric MPD is high, and that country income is associated with patient survival. On the other hand, the interpretation of interregional survival differences as found in this study remains complicated due to selection bias working in different directions. To reduce such bias, population-based registries are warranted.

Supplementary Material

Supplementary File (PDF)

Figure S1: DAG of the assumed relationships between the primary exposure (region) and the outcome (all-cause mortality on MPD).

Table S1: Overview of countries included in the different regions.

Article Information

Authors' Full Names and Academic Degrees: Sophie Ploos van Amstel, MD, Marlies Noordzij, PhD, Dagmara Borzych-Duzalka, MD, PhD, Nicholas C. Chesnaye, PhD, Hong Xu, MD, PhD, Lesley Rees, MD, Il-Soo Ha, MD, Zenaida L. Antonio, MD, Nakysa Hooman, MD, William Wong, MD, Karel Vondrak, MD, Yok Chin Yap, Hiren Patel, MD, Maria Szczepanska, MD, Sara Testa, MD, Monica Galanti, MD, Jameela A. Kari, MD, Charlotte Samaille, MD, Sevcan A. Bakkaloglu, MD, Wai-Ming Lai, MD, Luisa Fernanda Rojas, MD, Mabel Sandoval Diaz, MD, Biswanath Basu, MD, Alicia Neu, MD, Bradley A. Warady, MD, Kitty J. Jager, MD, PhD, and Franz Schaefer, MD, PhD.

Authors' Affiliations: IPNA Global RRT Registry, Department of Medical Informatics, Amsterdam UMC, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, the Netherlands (SPvA, MN, NCC, KJJ); Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg University, Heidelberg, Germany (DB-D, FS); Department of Pediatrics, Nephrology and Hypertension, Medical University of Gdansk, Gdansk, Poland (DB-D); Children's Hospital of Fudan University, Shanghai, People's Republic of China (HX); Great Ormond Street Hospital, London, United Kingdom (LR); Pediatrics Seoul, National University Children's Hospital, Seoul, South Korea (I-SH); Department of Pediatric Nephrology, National Kidney and Transplant Institute, Quezon City, Philippines (ZLA); Aliasghar Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran (NH); Starship Children's Hospital, Auckland, New Zealand (WW); University Hospital Motol, Prague, Czech Republic (KV); Department of Paediatrics, Hospital Tunku Azizah, Kuala Lumpur, Malaysia (YCY); Nationwide Children's Hospital, Columbus, OH (HP); Department of Pediatrics, Faculty of Medical Sciences, Zabrze, Medical University of Silesia, Katowice, Poland (MS); Fondazione Ospedale Maggiore Policlinico, Milan, Italy (ST); Roberto del Río Hospital, Santiago, Chile (MG); Pediatric Nephrology Center of Excellence, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia (JAK); Service de Néphrologie Pédiatrique, Hôpital Jeanne De Flandre, Lille, France (CS); Department of Pediatric Nephrology, School of Medicine, Gazi University, Ankara, Turkey (SAB); Department of Paediatric & Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong, People's Republic of China (W-ML); RTS, Medellin, Colombia (LFR); Hospital Infantil de Nicaragua "Manuel de Jesus Rivera," Managua, Nicaragua (MSD); NRS Medical College & Hospital, Kolkata, India (BB); School of Medicine, Johns Hopkins University, Baltimore, MD (AN); Children's Mercy, Kansas City, MO (BAW).

Address for Correspondence: Marlies Noordzij, PhD, Department of Medical Informatics, Amsterdam UMC, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Email: m.noordzij@amsterdamumc.nl

References

1. National Institute for Health and Care Excellence (NICE). Renal replacement therapy and conservative management. NICE guideline NG107. Accessed October 3, 2018. https://www.nice.org.uk/guidance/ng107

2. Vidal E, Chimenz R, Edefonti A, et al. a propensity-matched comparison of hard outcomes in children on chronic dialysis: the Italian Registry experience. *Ped Nephrol.* 2015;30(9).1552-1552.

3. Chesnaye NC, Schaefer F, Groothoff JW, et al. Mortality risk in European children with end-stage renal disease on dialysis. *Kidney Int.* 2016;89(6):1355-1362.

4. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2019;73(3)(suppl 1):A7-A8.

5. European Society of Pediatric Nephrology/European Renal Association and European Dialysis and Transplantation Association (ESPN/ERA-EDTA) Registry. Annual Report. 2018. Accessed October 7, 2019. https://espn-reg.org/files/AR2018.pdf

6. Mitsnefes MM, Laskin BL, Dahhou M, et al. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. *JAMA.* 2013;309(18):1921-1929.

7. Wood EG, Hand M, Briscoe DM, et al. Risk factors for mortality in infants and young children on dialysis. *Am J Kidney Dis.* 2001;37(3):573-579.

8. Kennedy SE, Bailey R, Kainer G. Causes and outcome of late referral of children who develop end-stage kidney disease. *J Paediatr Child Health.* 2012;48(3):253-258.

9. Warady BA, Abraham AG, Schwartz GJ, et al. Predictors of rapid progression of glomerular and nonglomerular kidney disease in children and adolescents: the Chronic Kidney Disease in Children (CKiD) cohort. *Am J Kidney Dis.* 2015;65(6):878-888.

10. Neu AM, Sander A, Borzych-Duzałka D, et al. Comorbidities in chronic pediatric peritoneal dialysis patients: a report of the international pediatric peritoneal dialysis network. *Perit Dial Int.* 2012;32(4):410-418.

11. Chesnaye NC, Schaefer F, Bonthuis M, et al. Mortality risk disparities in children receiving chronic renal replacement

therapy for the treatment of end-stage renal disease across Europe: an ESPN-ERA/EDTA registry analysis. *Lancet*. 2017;389(10084):2128-2137.

12. Ploos van Amstel S, Noordzij M, Warady B, et al. Renal replacement therapy for children throughout the world: the need for a global registry. *Pediatr Nephrol*. 2018;33(5):863-871.

13. International Pediatric Dialysis Network. About IPDN. Accessed December 5, 2018. http://www.pedpd.org

14. Borzych-Duzałka D, Bilginer Y, Soo Ha I, et al. Management of anemia in children receiving chronic peritoneal dialysis. *J Am Soc Nephrol*. 2003;24(4):665-676.

15. Schaefer F, Borzych-Duzalka D, Azocar M, et al. Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the International Pediatric Peritoneal Dialysis Network Registry. *Perit Dial Int*. 2012;32(4):399-409.

16. World Bank. World bank data. Accessed December 5, 2018. https://data.worldbank.org

17. World Health Organization. WHO Child Growth Standards. Accessed December 7, 2018. https://www.who.int/childgrowth/standards/en/

18. Noordzij M, Leffondré K, Van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant*. 2013;28(11):2670-2677.

19. Merlo J, Chaix B, Yang M, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: linking the statistical concept of clustering to the idea of contextual phenomenon. *J Epidemiol Community Health*. 2005;59(6):443-449.

20. Jager KJ, Zoccali C, MacLeod A, et al. Confounding: what it is and how to deal with it. *Kidney Int*. 2008;73(3):256-260.

21. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specifc mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1151-1210.

22. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016;387(10017):435-443.

23. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967.

24. Sinha A, Bagga A. Maintenance dialysis in developing countries. *Pediatr Nephrol*. 2015;30(2):211-219.

25. Jha V, Chugh KS. The practice of dialysis in the developing countries. *Hemodial Int*. 2003;7(3):239-249.

26. Prasad N, Gulati S, Gupta A, et al. Continuous peritoneal dialysis in children: a single-centre experience in a developing country. *Pediatr Nephrol*. 2006;21(3):403-407.