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ORIGINAL ARTICLE

Association between timing of dialysis initiation and clinical outcomes in the paediatric population: an ESPN/ERA-EDTA registry study

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ABSTRACT

Background. There is no consensus regarding the timing of dialysis therapy initiation for end-stage kidney disease (ESKD) in children. As studies investigating the association between timing of dialysis initiation and clinical outcomes are lacking, we aimed to study this relationship in a cohort of European children who started maintenance dialysis treatment.

Methods. We used data on 2963 children from 21 different countries included in the European Society of Pediatric Nephrology/European Renal Association–European Dialysis and Transplant Association Registry who started renal replacement therapy before 18 years of age between 2000 and 2014. We compared two groups according to the estimated glomerular filtration rate (eGFR) at start: eGFR $\geq$8 mL/min/1.73 m^2 (early

starters) and eGFR <8 mL/min/1.73 m^2 (late starters). The primary outcomes were patient survival and access to transplantation. Secondary outcomes were growth and cardiovascular risk factors. Sensitivity analyses were performed to account for selection- and lead time-bias.

Results. The median eGFR at the start of dialysis was 6.1 for late versus 10.5 mL/min/1.73 m^2 for early starters. Early starters were older [median: 11.0, interquartile range (IQR): 5.7–14.5 versus 9.4, IQR: 2.6–14.1 years]. There were no differences observed between the two groups in mortality and access to transplantation at 1, 2 and 5 years of follow-up. One-year evolution of height standard deviation scores was similar among the groups, whereas hypertension was more prevalent among late initiators. Sensitivity analyses resulted in similar findings.

Conclusions. We found no evidence for a clinically relevant benefit of early start of dialysis in children with ESKD. Presence of cardiovascular risk factors, such as high blood pressure, should be taken into account when deciding to initiate or postpone dialysis in children with ESKD, as this affects the survival.

Keywords: access to transplantation, cardiovascular complication, chronic kidney disease in children, early versus late dialysis, timing of dialysis initiation

INTRODUCTION

Criteria for starting dialysis in adults with end-stage kidney disease (ESKD) are the presence of uraemic symptoms in combination with abnormal biochemical findings, protein–energy wasting or fluid overload, which are difficult to manage conservatively [1, 2]. However, earlier studies proposed that starting dialysis at relatively high levels of estimated glomerular filtration rate (eGFR) (i.e. >10 mL/min/1.73 m^2) might be beneficial in terms of morbidity, mortality, nutritional status and quality of life [3–5]. In contrast, recent observational studies and a meta-analysis in adults with ESKD have shown that early initiation of dialysis was associated with harmful clinical outcomes [6, 7]. Furthermore, a recent observational study revealed that 25% of children starting renal replacement therapy (RRT) were late referrals requiring longer periods of dialysis before transplantation, but with similar survival rates to early referred patients [8]. In addition, the Initiating Dialysis Early and Late (IDEAL) study—the only randomized controlled trial (RCT) in adults—did not reveal improved survival or clinical outcomes with planned early dialysis initiation [9]. Lee *et al.* [10] confirmed these results and showed that hospitalization, cardiovascular events and dialysis-related complications were not different in adults who started dialysis early or late. Similarly, a recent paediatric study showed that early dialysis initiation has no benefit on important clinical outcome parameters, including left ventricular hypertrophy (LVH), inflammatory state and hospitalization [11].

As there is a paucity of paediatric data in this field, initiation of dialysis is nearly exclusively based on personal experience of paediatric nephrologists [12]. In 2001, an *ad hoc* European committee for elective peritoneal dialysis (PD) in children recommended dialysis initiation when measured or eGFR dropped to 10–15 mL/min/1.73 m^2 [13]. In 2006, the Kidney Disease Outcomes Quality Initiative guidelines stated that RRT in children should be considered when eGFR falls below 14 mL/min/1.73 m^2 and recommended when eGFR further falls below 8 mL/min/1.73 m^2 [14]. However, these recommendations were not based on evidence arising from paediatric studies.

A European Society for Pediatric Nephrology/European Renal Association–European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry report showed that eGFR at dialysis start was on average 10 mL/min/1.73 m^2 (5th and 95th percentile: 4–26.9 mL/min/1.73 m^2). Younger age, female sex and a short time between first visit to a paediatric nephrologist and start of RRT were the main determinants of lower eGFR at start of RRT [15], but the optimal time for dialysis initiation in children remains unclear.

We aimed to determine whether eGFR at start of maintenance dialysis was associated with different outcomes including mortality, access to transplantation, growth and control of cardiovascular complications in paediatric dialysis patients using data from the ESPN/ERA-EDTA Registry.

MATERIALS AND METHODS

Subjects

Data were collected through the ESPN/ERA-EDTA Registry. On an annual basis, the Registry collects individual patient data from all European children on RRT. Detailed information can be found elsewhere [16]. We included patients <18 years of age starting dialysis between 1 January 2000 and 31 December 2014. Only countries providing data on eGFR at dialysis start on at least 50% of patients were included, resulting in data contribution from 21 countries: Albania, Belarus, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, FYR of Macedonia, Georgia, Italy, Lithuania, Montenegro, the Netherlands, Poland, Portugal, Serbia, Slovenia, Slovakia, Turkey and the UK (Supplementary data, Table S1). Patients with congenital nephrotic syndrome of the Finnish type were excluded from the analyses as most of these patients initiate dialysis after bilateral nephrectomies with still good kidney function.

Definitions

All variables were determined according to local practice. eGFR (mL/min/1.73 m^2) was calculated using the revised Schwartz formula [17]. We classified timing of dialysis initiation as follows: eGFR at start ≥8 mL/min/1.73 m^2 (early initiation) or <8 mL/min/1.73 m^2 (late initiation). Primary renal disease (PRD) was categorized according to the ERA-EDTA coding system adapted for children [18].

Standard deviation scores (SDSs) for height were determined using recent national or European growth charts [19]. The body mass index was calculated as weight/height^2 and expressed according to chronological age for 0- to 1-year olds and according to height age for older children [20]. We defined cut-offs for underweight, obesity [21–23], hypertension [24, 25], anaemia [26] and hyperphosphataemia [27] according to international guidelines (Table 1).

Table 1. Cut-offs of cardiovascular risk factors

Risk factor	Cut-off	Guideline
Anaemia	Hb level below the 5th percentile for age and sex	NFK/KDOQI [25]
Hyperphosphataemia	Phosphate level (mg/dL)	European guidelines on prevention and treatment of renal osteodystrophy in children with chronic renal failure [26]
	0–2 years >7.4	
	3–5 years >6.5	
	6–12 years >5.8	
	13–17 years >4.5	
Underweight/obesity	BMI class based on age, sex and height adjusted criteria	World Health Organization (01 year) [22]
		International obesity task force (217 years) [20, 21]
Uncontrolled hypertension	SBP or DBP above 90th percentile for age, sex and height	KDOQI and KDIGO [23, 24]

[a]Hb, haemoglobin; NFK/KDOQI, National Kidney Foundation/Kidney Disease Outcomes Quality Initiative; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; KDIGO, Kidney Disease: Improving Global Outcomes.

Delayed referral to a paediatric nephrologist was defined as commencing dialysis within 3 months after their first appointment [8] and was only available for a subset of patients.

Statistical analyses

Data are shown as median and interquartile range (IQR) for continuous and as percentages for categorical variables. Descriptive statistics (Kruskal–Wallis test for continuous and Chi-square test for categorical variables) were used to explore differences in demographic and clinical characteristics.

Patient survival on dialysis and access to first kidney transplantation were assessed using a cumulative incidence competing risk approach and Cox proportional hazards regression. Adjustments were made for confounding effects of age at dialysis start, sex, PRD, dialysis modality and country [28].

All measurements (median: 2, IQR: 1–4 per patient) on cardiovascular risk factors from dialysis initiation until first transplant were included in the analyses. As multiple measurements within a patient are correlated, the prevalence of the cardiovascular risk factors and the associations between eGFR at dialysis initiation and likelihood of having these risk factors were calculated using generalized estimating equation models. Furthermore, linear mixed models with both a random intercept and slope for time since dialysis start were used to model height SDS in the first year after dialysis initiation.

To test the robustness of our results, we performed several sensitivity analyses. First, we examined the effect of lead time bias (i.e. additional survival time associated with early dialysis start that might result in artificial survival benefit) on patient survival. To correct for lead time, we estimated kidney function decline using linear mixed models in patients for whom data were available on eGFR at first visit to a paediatric nephrologist and at the start of dialysis ($n = 1168$). Using parameters from this model, we estimated the date when patients would have had an eGFR of 20 mL/min/1.73 m^2. Survival time was then counted from this date onward. For very young patients, we counted survival time from their date of birth.

Secondly, we repeated all analyses in patients with a sufficient time (at least 3 months) between first visit to a paediatric nephrologist and dialysis initiation.

Finally, we constructed a propensity score-matched cohort in order to reduce the effect of selection bias by ensuring an equal distribution of known patient characteristics between patients initiating dialysis early or late. The propensity score is the probability of starting dialysis early or late for each patient based on age, sex, PRD and initial dialysis modality. Patients with an eGFR below and above 8 mL/min/1.73 m^2 were matched on a one to one ratio.

All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Information on eGFR at start of dialysis was available for 2963 patients (Table 2). Most patients were male (56.1%), started dialysis due to congenital anomalies of the kidney and the urinary tract (CAKUT) (32.3%), and PD was the most frequent initial treatment modality (57.6%). Nearly half of the patients ($N = 1411$; 47.6%) had an initial eGFR <8 mL/min/1.73 m^2 (late starters). There were no significant differences in between countries concerning starting dialysis early or late, and the results by country were similar to the overall cohort patients' characteristics (Supplementary data, Table S2).

Median age at dialysis initiation was significantly lower for late, 9.4 (IQR: 2.6–14.1) years, than for early starters, 11.0 (IQR: 5.7–14.5) years ($P < 0.001$).

Late starters more often had CAKUT or an unknown diagnosis, whereas early starters more often presented with glomerulonephritis or hereditary nephropathies ($P < 0.001$).

Patient survival on dialysis

After a median follow-up of 1.3 (IQR: 0.7–2.3) years on dialysis 93 patients died, 48 (3.1%) after early and 45 (3.2%) after late initiation, resulting in an overall 1-, 2- and 5-year patient survival on dialysis of 98.2% [95% confidence interval (CI) 97.7–98.8], 96.3% (95% CI 95.4–97.2) and 91.1% (95% CI 88.7–93.7), respectively.

Causes of death were known for 61 patients (66%) and were not different between eGFR groups. Most patients died of infections (20%) or cardiac-related causes (15%).

Table 2. Patients characteristics

	eGFR classification (mL/min/1.73 m^2)		
	<8, $N = 1411$	≥8, $N = 1552$	Total, $N = 2963$
Male gender, *n* (%)	791 (56.1)	870 (56.1)	1661 (56.1)
Age at RRT (years),[a] median (IQR)	9.4 (2.6–14.1)	11.0 (5.7–14.5)	10.2 (4.2–14.3)
0–1, *n* (%)	311 (22.0)	188 (12.1)	499 (16.8)
2–5, *n* (%)	213 (15.1)	215 (13.9)	428 (14.4)
6–11, *n* (%)	369 (26.2)	455 (29.3)	824 (27.8)
12–19, *n* (%)	518 (36.7)	694 (44.7)	1212 (40.9)
Treatment at start,[a] *n* (%)			
HD	540 (38.3)	716 (46.1)	1256 (42.4)
PD	871 (61.7)	836 (53.9)	1707 (57.6)
PRD,[a] *n* (%)			
Glomerulonephritis	232 (16.4)	318 (20.5)	550 (18.6)
CAKUT	493 (34.9)	463 (29.8)	956 (32.3)
Cystic kidney disease	178 (12.6)	158 (10.2)	336 (11.3)
Hereditary nephropathy	90 (6.4)	135 (8.7)	225 (7.6)
Ischaemic renal failure	24 (1.7)	29 (1.9)	53 (1.8)
HUS	43 (3.1)	58 (3.7)	101 (3.4)
Metabolic disorders	47 (3.3)	46 (3.0)	93 (3.1)
Vasculitis	26 (1.8)	41 (2.6)	67 (2.3)
Miscellaneous	120 (8.5)	181 (11.7)	301 (10.2)
Unknown/missing	158 (11.2)	123 (7.9)	281 (9.5)
eGFR at start,[a] median (IQR)	6.1 (4.9–7.1)	10.5 (9.1–13.1)	8.2 (6.2–10.7)

[a]Statistically significant differences between the eGFR groups.
eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; PRD, primary renal disease; CAKUT, congenital anomalies of the kidney and urinary tract; HUS, haemolytic uraemic syndrome.

Mortality risk did not differ by eGFR at dialysis initiation [late versus early starters: hazard ratio (HR) = 1.00, 95% CI 0.66–1.51]. Following adjustment for age, sex, PRD, dialysis modality and country, the association remained non-significant: adjusted HR (aHR) late versus early initiation: 0.82, 95% CI 0.54–1.25.

Access to first kidney transplantation

The majority of patients received their first kidney transplant within 5 years after dialysis initiation: 82.0 and 81.4% of patients initiating dialysis early or late, respectively (Figure 1).

Likelihood to receive a first transplant within 1, 2 and 5 years after initiating dialysis was similar for late and early starters (HR late versus early starters: 0.93, 95% CI 0.81–1.08; 0.98, 95% CI 0.88–1.10; and 0.97, 95% CI 0.89–1.07, respectively) and remained similar in multivariable analysis (adjusted for age, sex, PRD, dialysis modality and country) (aHR = 1.00, 95% CI 0.86–1.16; aHR = 1.03, 95% CI 0.92–1.15; and aHR = 1.02, 95% CI 0.93–1.12, respectively).

Growth

Adjusted modelled growth patterns are shown in Figure 2. Height SDS at dialysis initiation was not different between the groups: mean height SDS was −1.79 (95% CI −1.88 to −1.71) and −1.76 (95% CI −1.84 to −1.68) for early or late starters, respectively, and showed a small, significant, but similar decrease in the year after dialysis initiation (−0.22 SDS for early and −0.24 SDS for late initiators).

Cardiovascular risk factors

After a median follow-up of 0.4 (IQR: 0.0–1.3) years, there were no differences in crude prevalence of anaemia and weight status by eGFR group (Figure 3). However, following adjustment, the prevalence of anaemia tended to be slightly higher among late starters [adjusted odds ratio (aOR) = 1.14, 95% CI

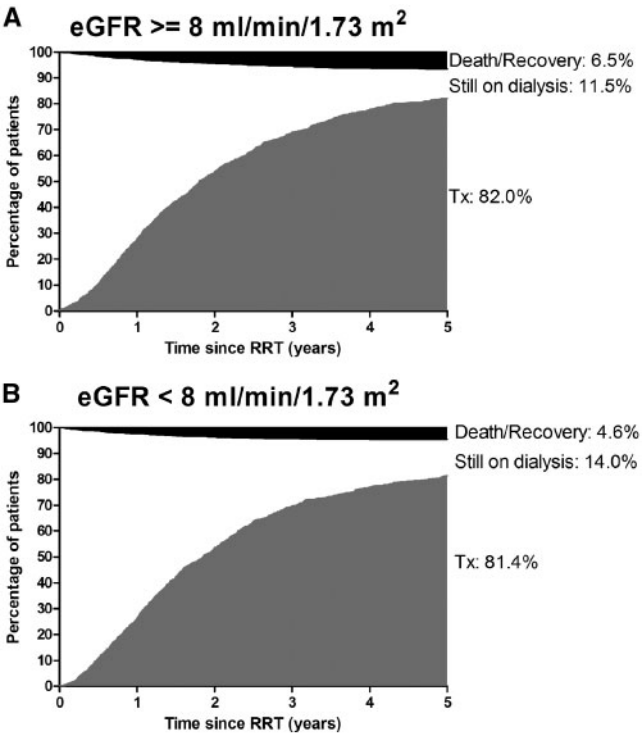

FIGURE 1: Cumulative incidence of receiving a renal transplant in the first 5 years after initiation of dialysis for patients starting dialysis early (eGFR ≥8 mL/min/1.73 m^2) (**A**) and patients starting dialysis late (eGFR <8 mL/min/1.73 m^2) (**B**). Tx, kidney transplantation.

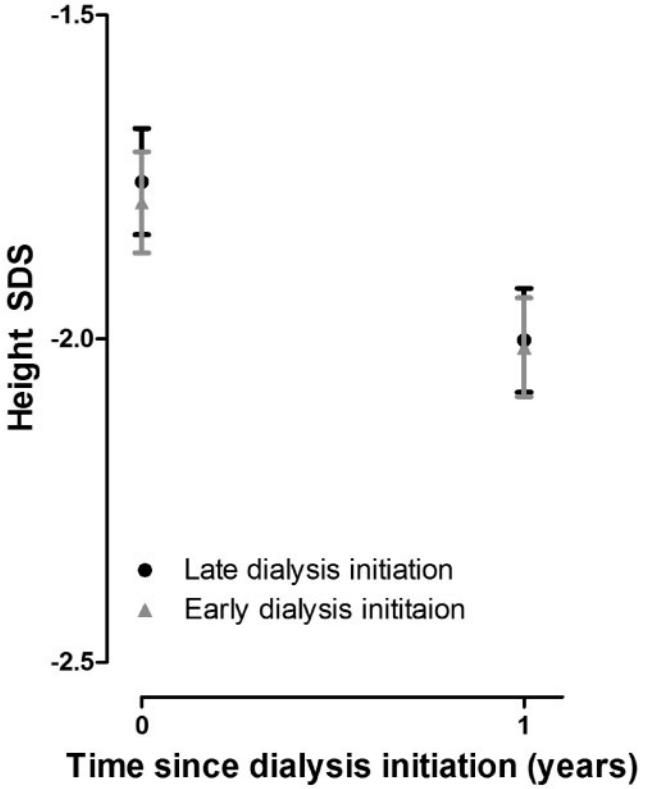

FIGURE 2: Modelled evolution of height SDS patients starting dialysis early (eGFR ≥8 mL/min/1.73 m^2) (grey triangles) and patients starting dialysis late (eGFR <8 mL/min/1.73 m^2) (black circles). Adjustments were made for age, sex, PRD and treatment modality.

0.99–1.32] compared with early starters (Table 3), whereas erythropoiesis-stimulating agent (ESA) use was around 90% in both groups.

Hypertension occurred more frequently in late (61%) than in early dialysis starters (54%), resulting in a significantly higher likelihood of having hypertension in late versus early starters (aOR = 1.35, 95% CI 1.15–1.58). Hyperphosphataemia was more frequently observed after early (28%) than after late (24%) initiation, resulting in a lower likelihood of hyperphosphataemia for late starters. However, this association did not remain significant in multivariable analysis (Table 2).

Delayed referral to a paediatric nephrologist

For a subgroup of patients ($n = 1527$; 837 early and 690 late starters), the date of the first appointment with a paediatric nephrologist was reported. Median time between this first appointment and start of dialysis was significantly lower for late starters: 5.1 (IQR: 0.1–33.9) months compared with 26.3 (IQR: 3.8–78.7) months for early starters ($P < 0.001$). Almost 50% of late starters initiated dialysis within 3 months from their first visit to a paediatric nephrologist (late referral), compared with 23% of early starters (Figure 4), resulting in an increased likelihood of delayed referral (aOR = 1.62, 95% CI 1.41–1.82; $P < 0.001$) in late starters, independent of age, sex and PRD.

Sensitivity analyses

Lead time-adjusted 5-year mortality risk was similar for early and late dialysis starters (aHR early versus late: 1.04, 95% CI 0.61–1.79), irrespective of country, age, sex, PRD and dialysis modality.

Among patients with sufficient time between first visit to a nephrologist and start of dialysis (≥3 months; $N = 1017$), there were no differences in 5-year mortality risk (aHR late versus early: 0.50, 95% CI 0.23–1.08) nor the 1-, 2- and 5-year likelihood of transplantation (aHR late versus early: 1.02, 95% CI 0.80–1.32; 0.94, 95% CI 0.78–1.15; and 0.97, 95% CI 0.82–1.14, respectively). Also, growth was similar between the two groups. Associations between eGFR and likelihood of anaemia and hypertension were similar for patients with at least 3 months between referral and dialysis initiation and the full cohort. Hyperphosphataemia and being underweight were less common among late starters (Table 3).

Additionally, analysing the propensity score-matched cohort ($N = 2494$) yielded no differences in mortality risk (aHR late versus early = 0.76, 95% CI 0.49–1.18) or likelihood of receiving a first transplant (aHR = 1.04, 95% CI 0.94–1.15) between patients starting dialysis early or late.

DISCUSSION

Our study suggests that in children with ESKD there is no clinical benefit of starting dialysis early. We found no significant associations of eGFR at dialysis initiation with either mortality, access to transplantation or growth after 1 year on dialysis.

In line with the IDEAL study, our results suggest that with careful clinical management of ESKD dialysis may be delayed for some patients until the eGFR drops below recommended values by KDIGO (<8 mL/min/1.73 m^2). Cooper *et al.* found no significant differences between early (eGFR 10–14 mL/min/1.73 m^2) and late start (5–7 mL/min/1.73 m^2) of dialysis for several outcomes including mortality, cardiovascular events, infections or hospitalization for infectious episodes and dialysis-related complications [9]. The 2014 Canadian Society of Nephrology clinical guidelines in adults recommend to start dialysis with first onset of a clinical indication or an eGFR decline to 6 mL/min/1.73 m^2 or less, whichever occurs first [29]. In an observational study of adults followed for 5–7 years, no survival benefit from early initiation of dialysis was found [30]. Moreover, after dialysis initiation, mortality was increased compared with patients not yet receiving RRT, possibly related to a decrease in residual renal function (RRF) after dialysis initiation. RRF has been shown to be an important predictor of survival of dialysis patients [31–34]. Unfortunately, the ESPN/ERA-EDTA Registry did not provide sufficient data on RRF.

One may speculate that late starters are less well prepared for transplantation, and therefore, might have a lower (short-term) access to transplantation, but our results did not confirm this hypothesis as likelihood of transplantation was similar in both groups. Even for patients starting dialysis late after a delayed referral to a paediatric nephrologist, chances of getting a transplant in the following 1-, 2- and 5-year period were the same as for early referrals.

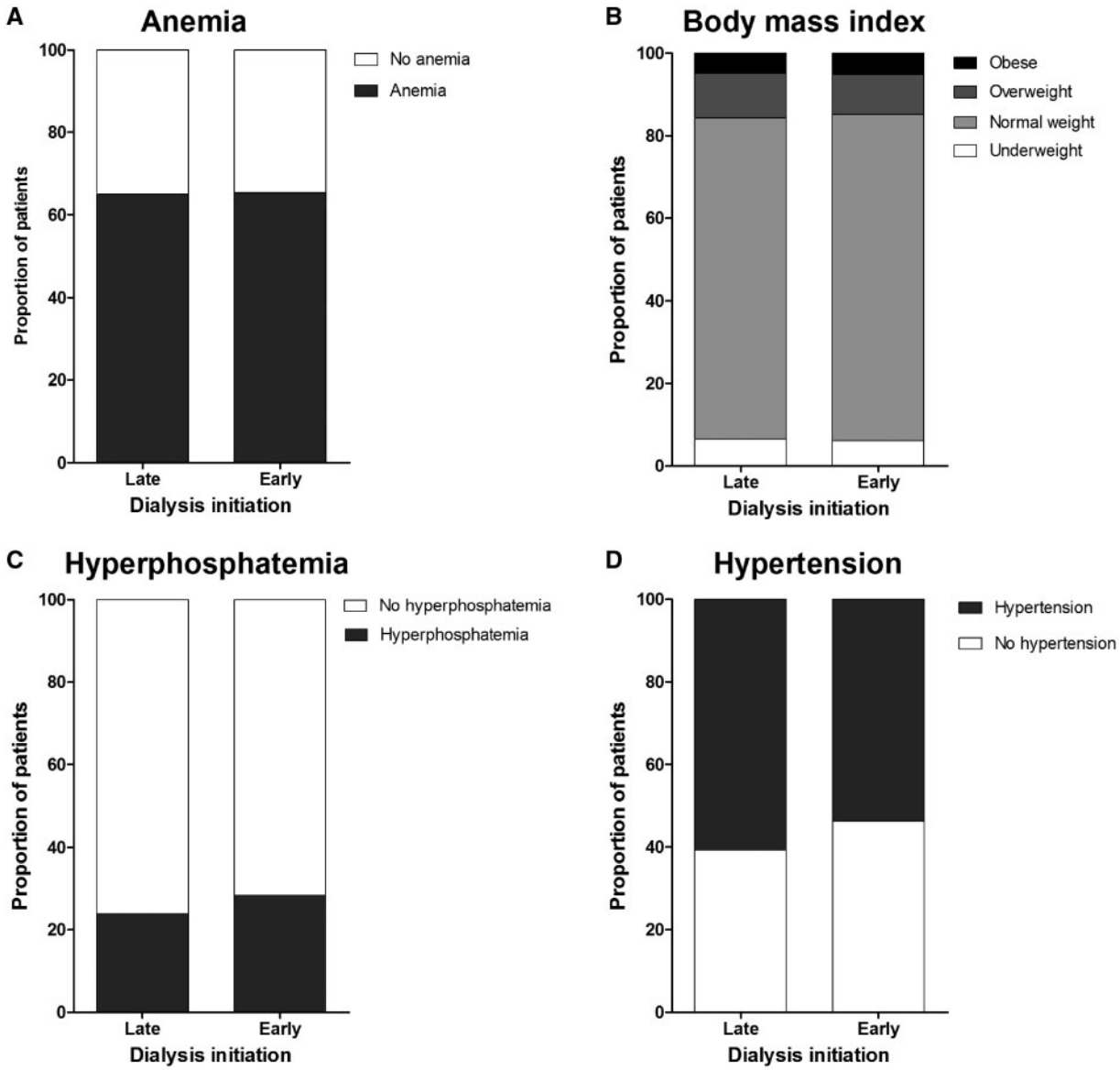

FIGURE 3: Prevalence of cardiovascular risk factors by eGFR category at dialysis initiation.

Height SDS was not different between patients starting dialysis early or late, both at start of dialysis and after 1 year. Similar results were found for patients with ≥3 months between first visit to a nephrologist and initiation of dialysis. Late starters were not exclusively patients who were referred late, from whom one suspect more growth retardation, but might also include patients conservatively treated so well that early dialysis start was apparently not needed. As long as urinary output is preserved, children can often be kept in a good clinical condition, even at a low eGFR, as long as they are kept in an anabolic state under a strict nutritional regime [35, 36], water and salt balance, and use medication to prevent chronic kidney disease-mineral and bone disorder and treat hypertension, if necessary growth hormone therapy [37]. It also explains the relatively large proportion of CAKUT patients among late starters, for whom we know there is a relatively slow renal function decline and long preservation of urine production.

Cardiovascular complications are common in children receiving dialysis, and are the leading cause of death (22% versus 3% in the general population) [38]. In a study of Turkish children on dialysis, even though LVH was more prevalent in the late start (eGFR <7 mL/min/1.73 m^2) than in the early start group (eGFR >10 mL/min/1.73 m^2), no significant differences were found for left ventricular mass index and LVH status [11]. We found that late starters were significantly more likely to have hypertension than early starters. We hypothesize that blood pressure control and fluid overload in oligoanuric patients are more difficult during conservative treatment, but as data on RRT are lacking, it is difficult to conclude with certainty. In case of resistant hypertension to conservative predialysis management and despite the well-known cardiovascular complications of dialysis, efforts to improve hypertension by dialysis might be a safer option until larger studies with longer follow-up are available. Late starters also tended to have a higher likelihood of anaemia despite similar ESA use among the eGFR categories.

PD was the most frequent initial modality without being statistically different from the haemodialysis (HD) group. Timing

Table 3. Odds ratios (95% CI) for cardiovascular risk factors (late versus early dialysis initiation)

	Total cohort			Sensitivity analysis: patients with at least 3 months between referral and dialysis start		
	eGFR <8 mL/min/1.73 m^2	eGFR ≥8 mL/min/1.73 m^2	P-value	eGFR <8 mL/min/1.73 m^2	eGFR ≥8 mL/min/1.73 m^2	P-value
Anaemia						
Unadjusted	0.99 (0.86–1.14)	1.00 (ref)	0.86	0.89 (0.68–1.16)	1.00 (ref)	0.38
Adjusted[a]	1.14 (0.99–1.32)	1.00 (ref)	0.08	1.23 (0.91–1.65)	1.00 (ref)	0.17
Hypertension						
Unadjusted	1.33 (1.14–1.55)	1.00 (ref)	<0.001	1.49 (1.12–1.99)	1.00 (ref)	0.007
Adjusted[a]	1.35 (1.15–1.58)	1.00 (ref)	<0.001	1.54 (1.13–2.11)	1.00 (ref)	0.007
Hyperphosphataemia						
Unadjusted	0.80 (0.66–0.96)	1.00 (ref)	0.02	0.58 (0.42–0.82)	1.00 (ref)	0.002
Adjusted[a]	1.11 (0.87–1.42)	1.00 (ref)	0.41	0.62 (0.44–0.88)	1.00 (ref)	0.007
Underweight						
Unadjusted	1.13 (0.89–1.44)	1.00 (ref)	0.31	0.72 (0.40–1.29)	1.00 (ref)	0.27
Adjusted[a]	0.95 (0.74–1.21)	1.00 (ref)	0.66	0.49 (0.25–0.94)	1.00 (ref)	0.03
Overweight						
Unadjusted	1.04 (0.88–1.23)	1.00 (ref)	0.66	1.02 (0.77–1.34)	1.00 (ref)	0.90
Adjusted[a]	1.11 (0.93–1.31)	1.00 (ref)	0.24	1.12 (0.84–1.49)	1.00 (ref)	0.43

[a]Adjusted for age, sex, primary renal disease and dialysis modality.
eGFR, estimated glomerular filtration rate;ref, reference category.

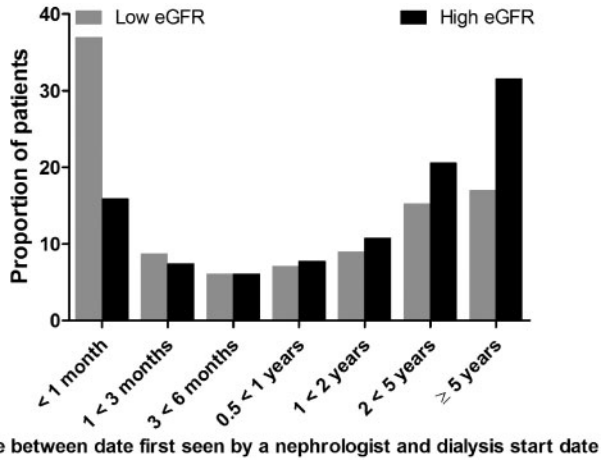

FIGURE 4: Distribution of patients by time between first appointment at the paediatric nephrologist and dialysis start for different eGFR at dialysis start.

of dialysis initiation was not associated with dialysis modality in this study. After adjustment for dialysis modality in all analyses, we found no significant differences in terms of survival, access to transplantation, growth and prevalence of cardiovascular risk factors between early and late starters. Interestingly, in another recent ESPN/ERA-EDTA Registry study from Chesnaye *et al.* [29], there was no significant difference in survival between patients treated initially with HD or PD, although the probability of receiving a transplant within 4 years after initiating RRT was higher in HD patients.

Late onset of dialysis was partly associated with late referral to a paediatric nephrologist. As a result, late starters initiated dialysis more often within the first month after their referral; however, our data did not reveal worse outcomes for late starters. Late referral might not only hinder the choice between dialysis modalities, but may also imply emergency HD using a temporary vascular access [39]. Similar to our study, UK Registry data showed no difference in transplantation rates after 1 year on dialysis [8], and a Polish study showed that even though children referred late presented with a worse general clinical status, the only significant difference with the group of early referred patients was the use of a temporary vascular access and a lower 3-year access to kidney transplantation [40].

The main strength of our study is that this is the first and largest study discussing this debatable issue in children from 21 European countries.

Due to its observational design, there are some limitations. First, GFR was estimated from plasma creatinine, resulting in possible misclassification due to variable creatinine levels depending on nutritional status. We acknowledge that the use of different methods of measuring creatinine might have introduced variation in the results, which is a limitation of our work. However, the variation in the measurements would likely have occurred to the same extent in all subgroups of patients (equally distributed among the two groups). This concept is called non-differential misclassification, and non-differential misclassification of a dichotomous exposure always biases towards the null.

Detailed clinical information on RRF, infections, reasons and number of hospitalizations was lacking. Despite the essentially complete Registry database, it is difficult to evaluate the overall condition of patients, and as such, the reasons for starting dialysis. As sicker patients are more likely to initiate dialysis early, this might have resulted in selection bias. We tried to correct for this by performing a sensitivity analysis among a propensity score-matched cohort, which did not show any survival advantage of early initiation. However, residual confounding of unmeasured variables remains possible. Also, analysing data of the patients with sufficient time before starting dialysis did not yield different findings.

Lead time bias might have contributed to better survival for early starters. However, after adjustment for lead time, patient

survival was similar among patients initiating dialysis early or late. Survivor bias could also have occurred, as individuals who died before starting dialysis are not included, and the ones that started dialysis late may have already survived for a longer period without requiring dialysis than those who started early, resulting in a possible overestimation of survival in this group. Nevertheless, our main analysis, as well as different sensitivity analyses, did not show any survival differences between children initiating dialysis early or late. The only way to fully avoid bias would be to conduct an RCT, which is not feasible or ethical in this small and heterogeneous patient population.

Similar to recent studies in adults and children, we did not find any association between timing of dialysis initiation and mortality, access to transplantation or growth in this large cohort of paediatric patients. The only difference observed was the prevalence of hypertension, which was more frequent in late starters, but there were no differences in the other cardiovascular risk factors.

Nevertheless, our data suggest that the decision to start dialysis in paediatric ESKD should not be merely based on eGFR, but should be a personalized decision in which benefits, burden, complexity and potential risks of dialysis are carefully balanced. Special attention for prevention of cardiovascular disease should be taken into account when opting for conservative treatment in children with a significantly low eGFR.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

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Supplemental material

Table S1. Number of patients per country

Country	N (%)
Albania	7 (0.2)
Belarus	65 (2.2)
Belgium	49 (1.7)
Bulgaria	33 (1.1)
Czech Republic	56 (1.9)
Estonia	2 (0.07)
Finland	86 (2.9)
France	450 (15.2)
FYR of Macedonia	7 (0.2)
Georgia	7 (0.2)
Italy	385 (13.0)
Lithuania	22 (0.7)
Montenegro	3 (0.1)
the Netherlands	131 (4.4)
Poland	248 (8.4)
Portugal	118 (4.0)
Serbia	30 (1.0)
Slovakia	33 (1.1)
Slovenia	21 (0.7)
Turkey	180 (6.1)
United Kingdom	1030 (34.8)
Total	**2963 (100)**

Table Number of patients per country starting dialysis early or late

Country	Early start N (%)	Late start N (%)
Albania	5 (71)	2 (29)
Belarus	35 (54)	30 (46)
Belgium	33 (67)	16 (33)
Bulgaria	9 (27)	24 (73)
Czech Republic	33 (59)	23 (41)
Estonia	2 (100)	0 (0)
Finland	36 (42)	50 (58)
France	237 (53)	213 (47)
FYR of Macedonia	5 (71)	2 (29)
Georgia	4 (57)	3 (43)
Italy	160 (42)	225 (58)
Lithuania	15 (68)	7 (32)
Montenegro	1 (33)	2 (67)
the Netherlands	62 (47)	69 (53)
Poland	160 (65)	88 (35)
Portugal	67 (57)	51 (43)
Serbia	11 (37)	19 (63)
Slovakia	23 (70)	10 (30)
Slovenia	8 (38)	13 (62)
Turkey	95 (53)	85 (47)
United Kingdom	551 (54)	479 (46)
Total	**1552 (52)**	**1411 (48)**