

Clinical outcomes and survival in pediatric patients initiating chronic dialysis: a report of the NAPRTCS registry

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Received: 16 November 2016 / Revised: 3 July 2017 / Accepted: 3 July 2017 / Published online: 31 July 2017
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Abstract

Background The 2011 annual report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry comprises data on 6482 dialysis patients over the past 20 years of the registry.

Methods The study compared clinical parameters and patient survival in the first 10 years of the registry (1992–2001) with the last decade of the registry (2002–2011).

Results There was a significant increase in hemodialysis as the initiating dialysis modality in the most recent cohort (42% vs. 36%, $p < 0.001$). Patients in the later cohort were less likely to have a hemoglobin <10 g/dl [odds ratio (OR) 0.68; confidence interval (CI) 0.58–0.81; $p < 0.001$] and height z-score <2 standard deviations (SD) below average (OR 0.68, CI 0.59–0.78, $p < 0.0001$). They were also more likely to have a parathyroid hormone (PTH) level two times above the upper limits of normal (OR 1.39, CI 1.21–1.60, $p < 0.0001$). Although hypertension was common regardless of era, patients in the 2002–2011 group were less likely to have blood pressure >90 th percentile (OR 1.39, CI 1.21–

1.60, $p < 0.0001$), and a significant improvement in survival at 36 months after dialysis initiation was observed in the 2002–2011 cohort compared with the 1992–2001 cohort (95% vs. 90%, respectively). Cardiopulmonary causes were the most common cause of death in both cohorts. Young age, growth deficit, and black race were poor predictors of survival.

Conclusions The survival of pediatric patients on chronic dialysis has improved over two decades of dialysis registry data, specifically for children <1 year.

Keywords End-stage renal disease · Hypertension · Cardiovascular disease · Anemia · Secondary hyperparathyroidism · Children

Introduction

The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) was established in 1987 to follow children and adolescents in North American who underwent renal transplantation. In 1992, the registry grew to include patients receiving hemodialysis (HD) or peritoneal dialysis (PD). In 2001, a NAPRTCS report describing the dialysis registry and trends in the management of pediatric patients on dialysis was published [1]. Since that report, the National Kidney Foundation sponsored Kidney Disease Outcomes Quality Initiative (KDOQI) composed updated clinical practice guidelines for managing patients on dialysis with the aim of improving quality of life (QoL) and lowering the high mortality rates in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [2, 3]. In this report, we present data from the second decade of the NAPRTCS dialysis registry and compare outcomes of patients who initiated dialysis in the first (1992–2001) vs the second (2002–2011) decade of

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the registry to assess the possible impact of KDOQI guidelines and advances in ESRD management.

Patients and methods

NAPRTCS involves both a data registry and a prospective trials division. For the registry division, participating centers throughout North America submit data on patients younger than 21 years at the time of enrollment with CKD, initiated dialysis, or received a kidney transplantation. The analysis focuses on children enrolled in the dialysis registry. Local institutional review board approval was obtained at each center for data entry.

The data collected from each center are sent on a voluntary basis to a data coordinating center. An initial registration form is completed, with follow-up status forms submitted 30 days and 6 months after initiation of dialysis and then every 6 months thereafter. An independent course of dialysis therapy is defined as a patient being maintained on a given modality for ≥ 30 days. The index course is dialysis occurring at the time of enrollment to NAPRTCS. As such, this analysis included only incident patients. One hundred and thirty-five centers contributed data to this analysis, of which, eight were Canadian. One hundred and thirty-three centers (including the eight Canadian) contributed data to the 1992–2001 and 92 (including eight Canadian) to the 2002–2011 cohorts. Of these, 90 centers provided data throughout both decades of the registry.

Standard univariate and multivariate statistical methods were used for data analysis. Continuous variables were assumed to follow a Gaussian distribution. Chi-squared tests were performed to compare era in binary and categorical endpoints. Kaplan–Meier product-limit estimates of time to dialysis modality termination, peritonitis incidence, and survival were created by era and were compared using the log-rank test. Multivariate logistic regression controlling for race, sex, age group, primary diagnosis, and modality was used to assess the effect of era on outcome parameters measured at 6 months after dialysis initiation. Outcome parameters were anemia stratified by hemoglobin groups of <10 g/dl vs. 10–12 g/dl vs. >12 g/dl. We controlled for erythropoietin-stimulating agent use and iron supplementation; hyperparathyroidism stratified by parathyroid hormone (PTH) more than twice the upper limits of normal (ULN) vs. less than twice the ULN controlling for vitamin D supplementation; elevated blood pressure stratified by blood pressure ≥ 90 th percentile vs. <90 th percentile and use of blood pressure medications; growth stratified by height standardized score < -2 SD vs. ≥ -2 SD, and for the use of growth hormones [4, 5]. If hemoglobin values were missing, comparable hematocrit ranges were used to evaluate anemia.

Patient survival was assessed in two ways: Death while on the first dialysis modality analyzes time of dialysis initiation to death, with censoring for dialysis termination or last follow-up.

The second method calculated patient survival from dialysis initiation to the last NAPRTCS follow-up, where patients are followed through registry changes (i.e., transplant or change in dialysis modality) until death or their last NAPRTCS visit. Cox regression analysis was used to estimate the effect of anemia, hyperparathyroidism, and hypertension and growth deficit at 6 months on survival while on dialysis. Patients were required to be followed for 6 months. This model was also adjusted for era, age group, race, gender, primary diagnosis, growth hormone use, and modality. To control for center-specific effects, a frailty analysis was performed in which each center was assumed to have a random effect that indicated the possibility of different baseline risks for patients at different centers. Unobserved center-level factors common to all patients from that center were accounted for in such an analysis. All statistical analysis was performed using the SAS System for Windows, v9.2 or v9.3 (SAS Institute, Cary, NC, USA).

Results

Patient and dialysis characteristics

Through 2011, 6482 patients were enrolled in the NAPRTCS dialysis registry. Of these, 4373 were enrolled from 1992 to 2001 and 2109 from 2002 to 2011. Selected demographic characteristics of both are presented in Table 1. There was no difference gender distribution between cohorts, with a slight male predominance at 55.8%. Compared to the 1992–2001 cohort, fewer white patients initiated dialysis in the 2002–2011 cohort (46% vs. 49%, $p = 0.006$). While mean age at dialysis initiation was similar in both cohorts (10.8 years and 10.7 years in earlier and later cohorts, respectively), more patients aged 6–12 (32% vs. 28%) were noted in the earlier cohort and more aged 13–17 (38% vs. 41%) in the later ($p = 0.002$). The leading cause of ESRD was renal aplasia/hypoplasia/dysplasia in the early cohort compared with focal segmental glomerulosclerosis (FSGS) in the later ($p = 0.047$). A statistically significant trend toward increased use of HD as the initial dialysis modality was noted between cohorts, with 36% of patients initiating renal replacement therapy on HD in the earlier compared with 42% in the later cohort ($p < 0.001$).

One hundred and thirty-five centers contributed data, with 133 contributing to the 1992–2001 and 92 to the 2002–2011 cohorts; 90 contributed to both decades. To minimize selection bias, demographic data from those centers only were compared, and results were similar to the entire cohort. We limited data to 90 centers and 5734 patients (3641 in 1992–2001 and 2093 in 2002–2011). There was no difference in gender distribution between cohorts ($p = 0.96$). Fewer white patients initiated dialysis in the 2002–2011 cohort (46% vs. 51%; $p = 0.001$). Mean age at dialysis was similar between cohorts, although more patients aged 6–12 (32% vs 28%)

Table 1 Characteristics of pediatric dialysis patients by dialysis initiation era

	Year of initiation			
	1992–2001		2002–2011	
	N	%	N	%
Total patients	4373	100.0	2109	100.0
Sex				
Male	2440	55.8	1176	55.8
Female	1932	44.2	933	44.2
Unknown	1	<0.1	0	0.0
Race				
White	2145	49.1	975	46.2
Black	1024	23.4	543	25.7
Hispanic	917	21.0	416	19.7
Other	287	6.6	175	8.3
Age at initiation (years)				
0–1	587	13.4	314	14.9
2–5	451	10.3	222	10.5
6–12	1379	31.5	585	27.7
13–17	1651	37.8	867	41.1
> 17	305	7.0	120	5.7
Missing	0	0.0	1	<0.1
Primary diagnosis				
Renal plasias	625	14.3	265	12.6
Obstructive uropathy	577	13.2	241	11.4
FSGS	613	14.0	325	15.4
Reflux nephropathy	152	3.5	74	3.5
Other	2068	47.3	1048	49.7
Unknown	338	7.7	156	7.4
Modality				
Peritoneal dialysis	2816	64.4	1221	57.9
Hemodialysis	1556	35.6	880	41.9
Missing	1	<0.1	8	0.4

FSGS focal segmental glomerulosclerosis

were enrolled in the earlier cohort and more aged 13–17 (38% vs 41%) in the later ($p < 0.002$). The leading cause of ESRD remained renal aplasia/hypoplasia/dysplasia in the early cohort compared with FSGS in the later ($p = 0.029$). A statistically significant trend toward increased use of HD as the initial modality was noted, with 35% of patients in the earlier group compared with 42% in the later cohort ($p < 0.001$).

Dialysis termination

As of the end of 2011, 5111 (795) registry patients terminated dialysis, leaving 1371 cases of active dialysis in the registry; 82% of cases terminated in the earlier cohort and 73% in the later ($p = 0.86$). Regardless of cohort, most terminations were

due to renal transplantation (69%) and subsequent changes in dialysis modality (17%) (Table 2) ($p = 0.79$). The primary reason for change in dialysis modality in the earlier cohort was excessive infection compared with patient/family choice in the later ($p = 0.039$). Regardless of cohort, PD (PD) patients were more likely to change modality due to infection, whereas HD dialysis patients were more likely to change modality due to patient choice (data not shown). Access failure, inadequate ultrafiltration, and inadequate solute clearance accounted for a combined 18% of modality changes in the earlier and 16% in the later era (Table 2) ($p = 0.68$). Similar results were observed when comparing the 90 centers that contributed data to both decades (data not shown).

Dialysis access

PD catheter characteristics are described in Table 3. A curled, single cuffed catheter with a straight tunnel and a lateral exit site was the most common access in the earlier cohort (15%) compared with a curled double-cuffed catheter with a swan-necked tunnel and downward-oriented exit site in the latter (20%) ($p < 0.001$). The proportion of catheters with a curled, intraperitoneal segment remained stable across both eras at >60% ($p = 0.61$), but more double-cuffed catheters were used in the more recent cohort (52% vs 41%; $p < 0.001$). In addition, catheters with a swan neck or curved vs straight tunnel were more common in the more recent group ($p = 0.023$). Transition away from upwardly and laterally oriented exit sites was also seen ($p = 0.011$). Similar results were observed when comparing data solely from the 90 centers that contributed data to both decades (data not shown).

In HD patients, regardless of era, central venous catheters were the most common form of access at the time of initiation (81% in the early cohort vs. 76% in the more recent cohort ($p = 0.75$). The use of jugular venous catheters was more common in the 2002–2011 (69% vs. 32%, respectively; $\chi^2 p < 0.001$). A corresponding decrease in the use of subclavian catheters was also noted in the later cohort (26% vs. 63%; $p < 0.001$). The use of arteriovenous fistulae and arteriovenous grafts at dialysis initiation remained low regardless of era, at 12.8% vs 11.3% and 9.5% and 2.1% ($p = 0.87$). Similar results were observed when comparing data solely from the 90 centers that contributed data to both decades (data not shown).

Clinical performance measures

Anemia management

At 6 months following initiation of dialysis, patients in the 2002–2011 cohort were more likely to have a hemoglobin >10 g/dl (79%) compared with the earlier cohort (67%) (Table 4). In fact, a logistic regression model adjusting for age, race, gender, primary diagnosis, modality, erythropoietin

Table 2 Dialysis terminations

	Year of Initiation			
	1992–2001		2002–2011	
	<i>N</i>	%	<i>N</i>	%
Terminated Dialysis Courses	3580	100.0	1531	100.0
Reason for Termination				
Patient Transplanted	2407	67.2	1133	74.0
Change of Modality	682	19.1	211	13.8
Death	102	2.8	15	1.0
Kidney Function Returned	115	3.2	34	2.2
Other/Unknown	274	7.7	138	9.0
Courses Changing Modality	682	100.0	211	100.0
Reason for Modality Change				
Excessive infection	222	32.6	48	22.7
Patient/family choice	127	18.6	56	26.5
Access failure	70	10.3	20	9.5
Inadequate ultrafiltration	38	5.6	7	3.3
Inadequate solute clearance	14	2.1	7	3.3
Excessive hospitalization (Dialysis related)	13	1.9	4	1.9
Excessive hospitalization (Other)	0	0.0	4	1.9
Other (medical)	93	13.6	24	11.4
Other (nonmedical)	27	4.0	15	7.1
Unknown	78	11.4	26	12.3

Table 3 Peritoneal dialysis access

	Year of Dialysis Initiation			
	1992–2001		2002–2011	
	<i>N</i>	%	<i>N</i>	%
Total Patients	2816	100.0	1221	100.0
Catheter				
Straight	832	29.5	226	18.5
Curled	1707	60.6	795	65.1
Toronto	20	0.7	4	0.3
Presternal	200	7.1	14	1.1
Other	11	0.4	84	6.9
Unknown/Missing	46	1.6	98	8.0
Cuffs				
One	1588	56.4	471	38.6
Two	1165	41.4	633	51.8
Unknown/Missing	63	2.2	117	9.6
Tunnel				
Swan necked/curved	696	24.7	648	53.1
Straight	2044	72.6	457	37.4
Unknown/Missing	76	2.7	116	9.5
Exit site orientation				
Up	404	14.3	103	8.4
Down	867	30.8	415	34.0
Lateral	1216	43.2	339	27.8
Unknown/Missing	329	11.7	364	29.8

stimulating agent (ESA) use, and iron supplementation showed that patients in the 2002–2012 cohort were more likely to maintain a hemoglobin >12 g/dl [odds ratio (OR) 2.06; confidence interval (CI) 1.77–2.39; $p < 0.001$] multivariate analysis showed those patients were less likely to have hemoglobin <10 g/dl (OR 0.68; CI 0.58–0.81; $p < 0.001$) compared with those initiating dialysis between 1992 and 2001. ESA use was common in both cohorts (93% and 91%, respectively). Iron supplementation remained steady over the years (79% in 1992–2001 vs. 78% in 2002–2011); there was, however, a shift from iron supplementation orally (75% vs. 58%) to IV (12% to 24%) between the early and later eras.

Hyperparathyroidism

In the NAPRTCS registry, PTH levels are reported as <2× or >2× the ULN. At 6 months following dialysis initiation, there was a trend toward higher PTH levels in the 2002–2011 cohort, with 61% of patients with a PTH >2× the ULN compared with 54% in the earlier cohort (Table 4). More patients were also noted to have a PTH level <2× the ULN in the 1992–2001 group (46% vs. 39%). A logistic regression model controlling for race, gender, primary diagnosis, modality, and vitamin D

supplementation confirmed that patients in the 2002–2012 were more likely to have a PTH >2× the ULN (OR 1.39, CI 1.21–1.60, $p < 0.001$).

Hypertension management

Hypertension is defined in the registry by a blood pressure ≥90th percentile of standardized blood pressures for age, height, and gender according to the the Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents [4]. More patients in the 1992–2001 cohort were ≥90th percentile 6 months after dialysis initiation compared with the 2002–2011 group (64% vs. 58%). Similar results were obtained using the 95th and 99th percentiles for age, height, and gender; More patients in the later cohort were on antihypertensive therapy (59% vs 53%) (Table 4). A significant number of patients remained hypertensive in the 2002–2011 group (Table 4), but logistic regression modeling showed that they were less likely to be hypertensive than patients who initiated dialysis between 1992 and 2001 (OR 0.71, CI 0.62–0.81, $p < 0.001$). Results were similar

Table 4 Clinical performance measures by dialysis initiation era

	Year of Dialysis Initiation				Logistic Regression Model	
	1992–2001		2002–2011		Reference group: 1992–2001 era Comparison group: 2001–2012 era	
	<i>N</i>	%	<i>N</i>	%	OR (95% CI)*	<i>P</i> -value
Total	2785	100.0	1558	100.0		
Anemia						
Hemoglobin <10 g/dl	869	32.8	312	20.4	0.68 (0.58–0.81)	<0.001
Hemoglobin 10–12 g/dl	1201	45.3	616	40.2	reference group	
Hemoglobin >12 g/dl	580	21.9	604	39.4	2.06 (1.77–2.39)	<0.001
Hyperparathyroidism						
PTH <2X ULN	1050	45.8	513	38.8	Reference group	
PTH >2X ULN	1242	54.2	809	61.2	1.39 (1.21–1.60)	<0.001
Hypertension						
BP <90th percentile	923	35.8	591	41.9	Reference group	
BP ≥90th percentile	1655	64.2	820	58.1	0.71 (0.62–0.81)	<0.001
Growth deficit						
Height > -2 SD	1547	59.6	977	67.2	Reference group	
Height ≤ -2 SD	1051	40.5	477	32.8	0.68 (0.59–0.78)	<0.001

Logistic regress models adjusted for age, race, gender, primary diagnosis categories, and modality; anemia model adjusted for erythropoietin and iron supplementation; hyperparathyroidism model adjusted for vitamin D supplementation; hypertension model adjusted for antihypertension medication use; growth model adjusted for growth hormone use;

PTH parathyroid hormone, *ULN* upper limits of normal, *BP* blood pressure, *SD* standard deviation, *OR* odds ratio, *CI* confidence interval

*Odds ratios reflect the odds in the comparison group (2001–2012 era) compared to the reference group (1992–2001 era)

when patients on PD and HD were compared. Regardless of era, a higher percentage of HD patients (64%) were on anti-hypertensive therapy compared with those on PD (51%).

Growth deficit

The use of recombinant human growth hormone (rhGH) at 6 months postdialysis initiation remained low, at 17% in the later and 12% in the earlier cohort. Standardized height z-scores were calculated by adjusting for the appropriate population-, age-, and sex-specific levels for the normal population provided by the 2000 US National Institutes of Health Centers for Disease Control growth charts [5]. The earlier cohort demonstrated a mean (SD) standardized z-score of -1.73 ± 1.63 [with 41% < -2 standard deviation scores (SDS)] compared with a significant improvement in mean standardized z-score in the later cohort of -1.49 ± 1.60 (with 33% < -2 SDS) (Table 4). Patients were less likely to have a height standardized z-score <2 SDS in the 2002–2012 compared with the 1992–2001 era (OR 0.68, CI 0.59–0.78, $p < 0.001$, Table 4).

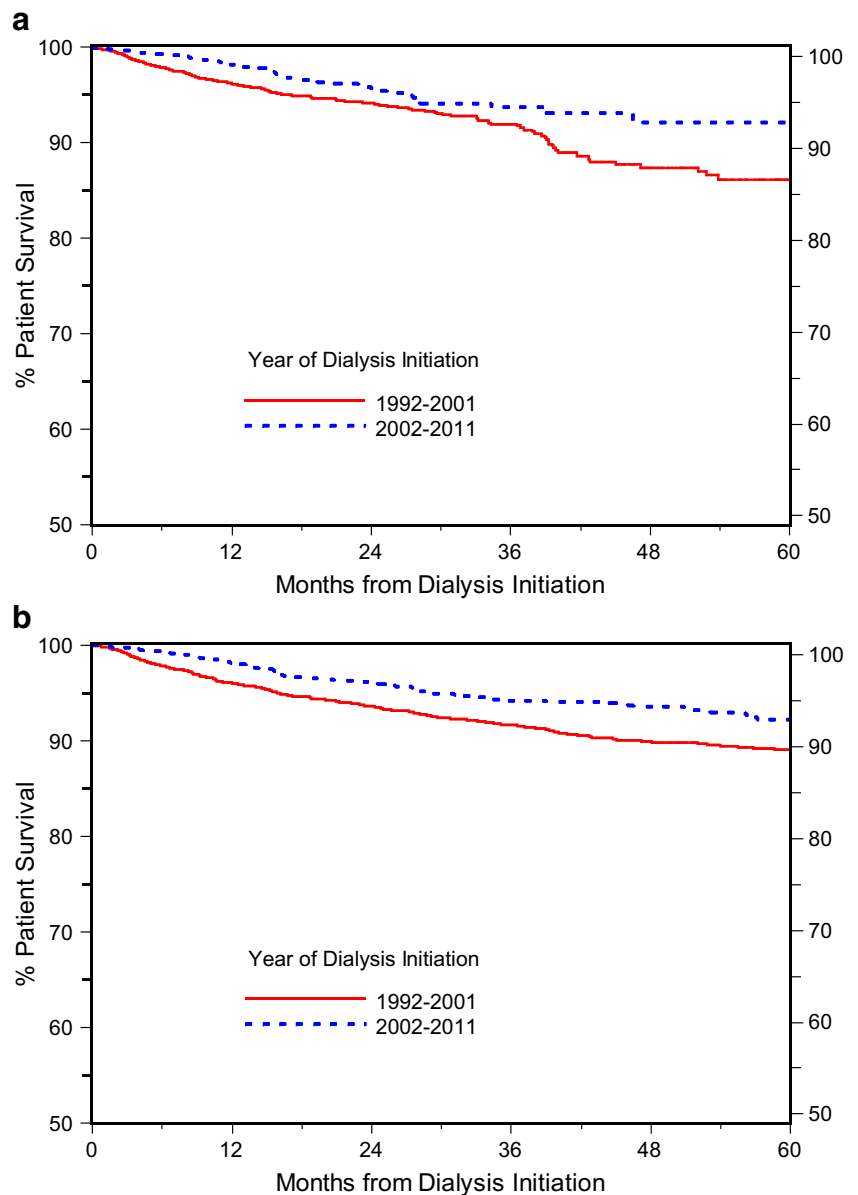
Dialysis adequacy

Patient Kt/v data has only been collected by the registry since 2002, so dialysis eras were not compared for this parameter. At 6 months postdialysis initiation, 73% of patients on HD maintained a Kt/v >1.2 and 56% on PD a Kt/V of ≥2.0. When patients on PD and HD with goal Kt/v were compared to those below the goal, there was no difference in survival.

Patient survival

Of the 6482 patients in the dialysis registry, 539 (8.3%) died. Survival while on dialysis and overall survival (OS) are shown in Fig. 1a, b. Survival estimates were 98%, 96%, and 95% at 12, 24, and 36 months, respectively, in the 2002–2011 group compared with 95%, 91%, and 90% at 12, 24, and 36 months, respectively in the 1992–2001 cohort (Fig. 1a). Across both cohorts, patient survival remains lowest for patients <1 year at the time of initiation of dialysis, but there was a significant improvement in survival in the later cohort ($p < 0.001$) (Fig. 2).

Fig. 1 Patient survival in the dialysis registry. **a** Patients on their first course of dialysis, with censoring for dialysis termination or last-follow-up. **b** Patients who initiated dialysis in the registry and were followed through registry changes, including transplant or change in dialysis modality, until death or their last follow-up



The leading specified cause of death remained cardiopulmonary regardless of age group (114/538, 21.1%); there was no difference in cause of death by time period (Table 5). At 6 months, there were 4343 dialysis patients still alive and receiving dialysis. Of those, 3389 had complete data on all covariables and were included in Cox regression analysis. In this group of 3389, there were 107 subsequent deaths (3.2%). In the adjusted model, young age, growth deficit, and black race were all poor predictors of survival (Table 6). Similar results were obtained using frailty analysis to model correlations between failures of the same cluster by using a random component for the hazard function. In this analysis, “center” was the random cluster; when

it was added to the Cox regression model, it was not significant, and results of the other covariates were similar to the initial model (Table 7).

Discussion

This report summarizes data on >6000 children enrolled in the NAPRTCS dialysis registry since 1992. The results indicate improvements in several key clinical performance measures, such as anemia, growth, and blood pressure control, over the 2002–2011 decade collection compared with the 1992–2001 time period. A higher percentage of patients in the later cohort maintained a hemoglobin >10 g/dl at 6 months. The effects of

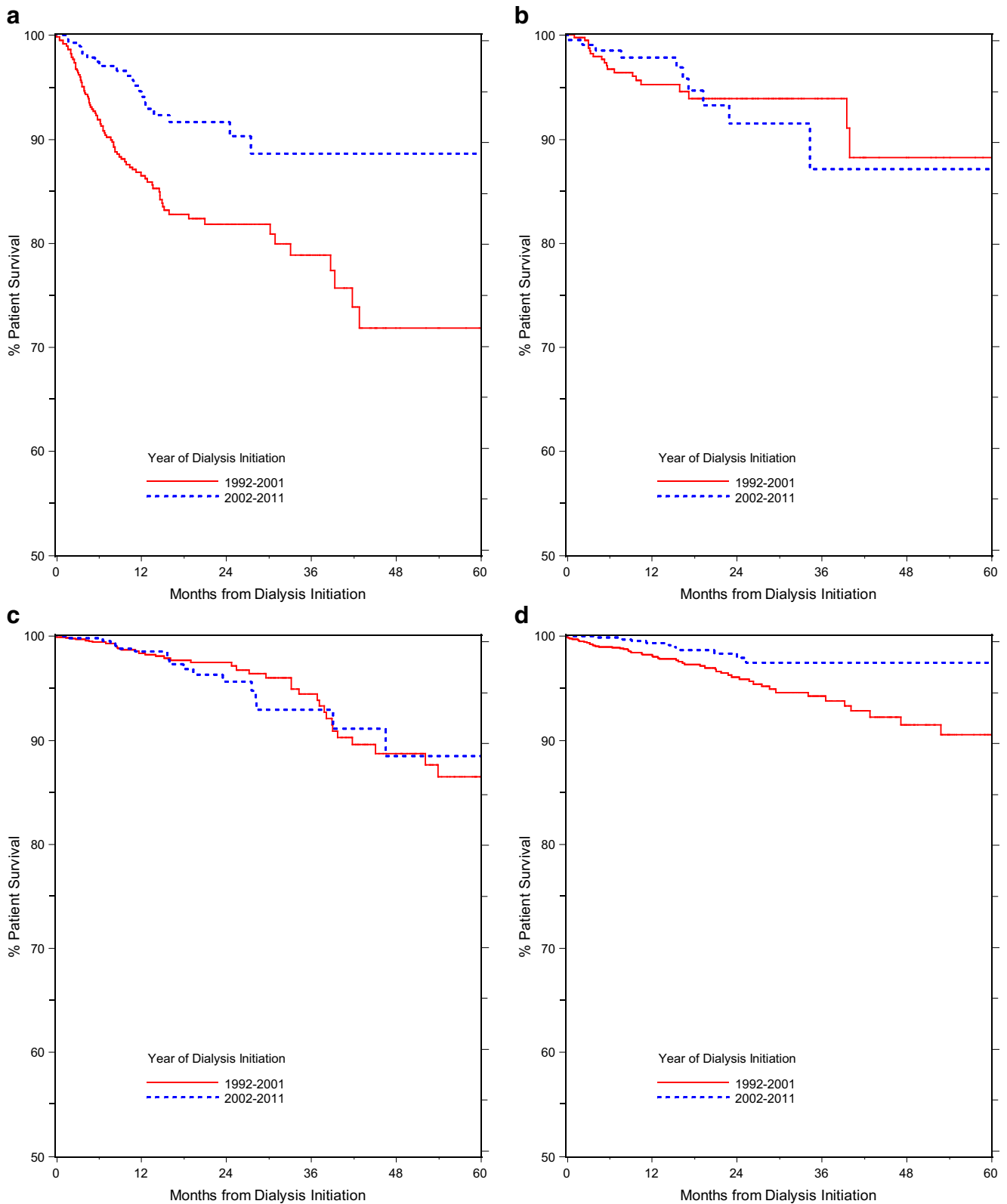


Fig. 2 Improvement in patient survival in the dialysis registry based on age at initiation by era. **a** 0–1 year ($p < 0.001$); **b** 2–5 years ($p = 0.64$); **c** 6–12 years ($p = 0.90$); **d** 13 years ($p = 0.002$)

uncontrolled anemia in pediatric patients on dialysis are well documented, including decreased QoL, development of left

ventricular hypertrophy, increased risk of hospitalization, and increased mortality rates [6, 7]. A study from the

Table 5 Causes of death by era

	Year of Dialysis Initiation			
	1992–2001		2002–2011	
	<i>N</i>	%	<i>N</i>	%
All Deceased Patients	439	100.0	99	100.0
Cause of Death				
Infection, viral	13	3.0	3	3.0
Infection, bacterial	48	10.9	11	11.1
Infection, not specified	32	7.3	3	3.0
Cancer/malignancy	30	6.8	6	6.1
Cardiopulmonary	94	21.4	20	20.2
Hemorrhage	19	4.3	2	2.0
Recurrence	6	1.4	1	1.0
Dialysis-related complications	14	3.2	6	6.1
Other	122	27.8	23	23.2
Unknown	61	13.9	24	24.2

International Pediatric Peritoneal Dialysis Network noted that a hemoglobin <11 g/dl was associated with increased mortality [8]. A separate study of 677 adolescents on HD using data from the US Centers for Medicare and Medicaid Services End-Stage Renal Disease Clinical Performance Measures (CMS-ESRD-CPM) project found that patients who did not achieve a hemoglobin target of 11–12 g/dl were at increased risk for

mortality [9]. Using data from the US Renal Data System (USRDS), Dahlinghaus et al. found that increased dose of ESA (used as a marker of more significant anemia) was associated with increased hospitalizations and mortality [10]. Cognizant of these adverse outcomes in children with lower hemoglobin levels, current KDOQI and Kidney Disease–Improving Global Outcomes (KDIGO) guidelines recommend that a hemoglobin level of 11–12 g/dl should be achieved in infants, children, and adolescents on dialysis [2]. It is not clear whether these therapeutic targets are optimal, since there have been no prospective trials to evaluate the effect of different higher hemoglobin targets on outcomes in children and adolescents. In the absence of such data, current targets are mostly based on adult studies showing that a hemoglobin >13.5 g/dl was associated with increased cardiovascular and cerebrovascular events [11].

Similar to the improvement in anemia seen over time, a higher percentage of patients in the more recent cohort maintained blood pressures <90th percentile for age, height, and gender compared with the earlier cohort. In addition, more patients in the recent era were on antihypertensive therapy. However, registry data confirms previous findings that hypertension in the dialysis population remains undertreated, with >50% of registry patients continuing to demonstrate blood pressures >90th percentile despite most pediatric nephrologists intending to maintain lower targets [12]. Since hypertension is associated with intermediate outcomes on cardiovascular health, including development of left ventricular

Table 6 Predictors of 6-months patient survival after dialysis initiation

Variable	Reference Group	Comparison Group	HR	95% CI	<i>P</i> value
Age (overall <i>p</i> < 0.001)	≥13 years	0–1	4.32	2.40–7.75	<0.001
		2–5	2.20	1.06–4.59	0.035
		6–12	2.00	1.17–3.41	0.011
Race (overall <i>p</i> < 0.135)	White	Black	1.58	1.01–2.47	0.046
		Hispanic	0.85	0.48–1.52	0.592
		Other	1.13	0.51–2.52	0.770
Gender	Male	Female	1.24	0.83–1.84	0.297
Primary Diagnosis (overall <i>p</i> < 0.010)	Renal plasias	FSGS	0.47	0.17–1.31	0.150
		Obs uro	0.78	0.36–1.66	0.513
		Reflux neph	0.42	0.06–3.14	0.395
		Other/unk	1.60	0.95–2.72	0.080
Modality	PD	HD	0.92	0.57–1.49	0.730
Dialysis era	2002–2011	1992–2001	1.18	0.76–1.83	0.463
Anemia	No	Yes	1.13	0.75–1.71	0.554
Hyperparathyroidism	No	Yes	0.90	0.61–1.32	0.574
Hypertension	No	Yes	0.89	0.60–1.33	0.574
Growth deficit	No	Yes	2.08	1.39–3.12	<0.001

FSGS focal segmental glomerulosclerosis, Obs uro obstructive uropathy, Reflux neph reflux nephropathy, Unk unknown, PD peritoneal dialysis, HD hemodialysis, HR hazard ratio, CI confidence interval

Table 7 Predictors of patient survival (>6 months) after dialysis initiation, with “center” as a random effect

Variable	Reference Group	Comparison Group	HR	95% CI	Adjusted <i>p</i> value
Age (overall <i>p</i> < 0.001)	≥13 years	0–1	4.42	2.45–7.97	<0.001
		2–5	2.22	1.06–4.63	0.034
		6–12	1.99	1.17–3.40	0.012
Race (overall <i>p</i> < 0.178)	White	Black	1.54	0.98–2.43	0.060
		Hispanic	0.87	0.48–1.55	0.620
		Other	1.10	0.49–2.48	0.806
Gender	Male	Female	1.24	0.83–1.85	0.288
Primary Diagnosis (overall <i>p</i> < 0.010)	Renal plasias	FSGS	0.47	0.17–1.31	0.149
		Obs uro	0.78	0.37–1.68	0.530
		Reflux neph	0.42	0.06–3.16	0.398
		Other/unk	1.60	0.94–2.72	0.081
Modality	PD	HD	0.92	0.57–1.51	0.744
Dialysis era	2002–2011	1992–2001	1.20	0.77–1.87	0.424
Anemia at 6 months	No	Yes	1.13	0.75–1.71	0.567
Hyperparathyroidism at 6 mo.	No	Yes	0.90	0.61–1.32	0.576
Hypertension at 6 months	No	Yes	0.90	0.60–1.33	0.583
Growth deficit at 6 months	No	Yes	2.06	1.37–3.10	<0.001
Center (random variable)					0.339

FSGS focal segmental glomerulosclerosis, Obs uro- obstructive uropathy, Reflux neph reflux nephropathy; unk- unknown, PD peritoneal dialysis, HD hemodialysis, HR hazard ratio, CI confidence interval

hypertrophy and cardiac dysfunction, ongoing improvements in hypertension management may lead to ongoing improvements in survival [13].

Data from the registry show that a higher percentage of patients in the latest era had a PTH level twice the ULN, suggesting that providers are tolerating higher PTH levels than in previous years. As with hemoglobin, the ideal serum PTH level in pediatric patients on dialysis is not known, but there has been increasing attention to data suggesting the need to allow a degree of hyperparathyroidism to encourage normal bone turnover; this is reflected in PTH targets found in KDOQI and KDIGO guidelines [14]. Maintaining a normal PTH level in the setting of dialysis is thought to lead to adynamic bone disease, but data also suggest that very high levels are linked to both bone and cardiovascular disease [15] and are specifically associated with impaired linear growth in children and in the development of myocardial fibrosis in some in vitro models [16, 17]. Despite the trend toward tolerating higher PTH levels, the percentage of doctors prescribing vitamin D in both oral and intravenous forms remained unchanged across eras.

This analysis noted changes in several other aspects of pediatric dialysis care over the past 20 years, including initial modality and access type. Specifically, more patients chose HD in the latest era, continuing a trend noted in a prior NAPRTCS registry report [1] and likely related in part to increased availability of HD services for children since the earlier era. Several factors other than availability are known to influence dialysis modality selection, including patient age,

adherence to a prescribed home regimen, and patient/parental preference [7]. In fact, patients in the more recent cohort were more likely to change modality due to family choice, as opposed to medical complications such as excessive infection. The jugular vein remained the most common location for percutaneous HD catheters, similar to prior publications, and the use of arteriovenous (AV) grafts or AV fistulae at the time of dialysis initiation remain uncommon in children, despite guidelines emphasizing the benefits of permanent access over catheters. In children, numerous obstacles may exist to placing more definitive dialysis access, including technical difficulty given smaller blood vessels, fewer pediatric vascular-access specialists, and patient/family preference due to hopes to accomplish a renal transplant quickly. In terms of PD access, the increase in placement of swan-necked/curved, double-cuffed, downwardly oriented catheters is consonant with current recommendations that are largely based on data suggesting lower annualized peritonitis rates and longer times to first peritonitis episodes, with such access [18].

Registry data also demonstrates a difference in ESRD etiology between eras. Supplanting renal dysplasia and hypoplasia, FSGS is now the most common primary diagnosis. Recent reports indicate that the incidence of FSGS has increased over the last two decades and is especially problematic in black and Hispanic children [19]. Such children are less likely than non-Hispanic white children to be transplanted, and, as a result, they often spend longer periods on dialysis. There can also be a degree of medical-provider and parental reluctance to

transplant children with FSGS given their high risk for recurrent disease, especially in children who may already have lost a renal allograft due to recurrence. A recent registry report from European centers noted that Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) were the most common cause of renal disease [20]. These discrepant findings may be due to several factors. The current registry included patients until the age of 21, compared with 14 in the European registry. Renal disease etiology was classified using different terminology: e.g. the European registry classified patients into CAKUT or glomerulonephritis groups, whereas the NAPRTCS registry allows data entry using multiple diagnoses that would fall under these more general disease categories. Finally, sampling bias may be present based on how individual centers enter data, as “Other” was the most commonly entered diagnosis in the NAPRTCS registry.

Registry data used in our report confirms an improvement in survival in children requiring chronic dialysis, which has recently been noted elsewhere [21]. In the NAPRTCS dialysis registry analysis, younger age, black race, and growth deficit were predictors of decreased survival, consistent with findings from several other registries, including USRDS [21–26]. Several studies have demonstrated an association between younger age and decreased survival [27, 28], though it is heartening that this NAPRTCS dialysis registry data shows significantly increased survival in children starting dialysis at <1 year of age between 2002 and 2011, compared with the earlier decade. Although speculative, improved dialysis equipment designed or adapted for smaller children, better surgical techniques, and improved clinical experience may have contributed to these improvements.

In prior analysis of NAPRTCS data, race influenced both the choice of modality and timing of initiation [29, 30]. Additional analysis focusing on clinical performance measures in PD patients has suggested that black patients are less likely to meet hemoglobin targets or achieve goal serum albumin levels [31, 32]. Differences have not been observed in dialysis adequacy [27, 31]. Because of its cross-sectional design, a causal relationship was not established in our analysis, but poor nutrition and heightened inflammation or differences in ESRD etiology are all possible factors influencing meeting these targets and which may account for differences in survival.

Growth deficit also negatively affected survival. A prior NAPRTCS study examining 2306 pediatric patients who initiated dialysis between 1992 and 2000 showed that poor growth in predialysis CKD was suggestive of a more complicated course following initiation [27]. Ku et al. recently analyzed data on 13,218 children in the USRDS and found that both short and tall stature increased mortality risk [28]. In prior studies, short stature in children with CKD and ESRD was associated with nonadherence to medical therapy, impaired access to care, and illness severity [33–35]. Growth failure in pediatric CKD is also associated with increased

hospitalizations, poor school performance, and lower self-esteem [36, 37]. Although height improvement in the most recent dialysis cohort is reassuring, it remains concerning that only a small percentage of patients are on rhGH in the later cohort, a finding also observed in a prior NAPRTCS report [1]. Several barriers to the use of rhGH have been cited, including severe hyperparathyroidism, difficulty obtaining insurance approval, and noncompliance. However, rhGH is not the only option: recent studies demonstrated that aggressive nutritional management and use of biocompatible dialysate can improve growth [33, 38]. Intensified HD and hemodiafiltration protocols have also been useful [39, 40].

Since the NAPRTCS dialysis registry is a voluntary database, sampling bias is present and could influence results from our analysis. Specifically, 135 centers contributed data, eight of which were Canadian; 133 centers (including the eight Canadian) contributed to the 1992–2001 cohort and 92 (including the eight Canadian) to the 2002–2011. Therefore, there were fewer centers participating in the registry in the last decade. Reasons for this change are not certain; however, all centers enter data retrospectively, and there is no restriction on timing for data entry. Therefore, there may be some differences due to delays in data entry. In addition, centers were previously provided a stipend for data entry. To control for these effects, frailty analysis was conducted, and results of the adjusted model were similar. Moreover, demographic data did not change significantly when data only from centers that contributed to both decades were analyzed. Finally, data do not provide causation, although they do provide important associations. Specifically, given the relative rarity of pediatric ESRD, the NAPRTCS dialysis registry serves as an important source of information on children with ESRD as they transition between different treatment requirements. Given large number of pediatric centers contributing data to the registry allows a better understanding of how these children are cared for in pediatric dialysis units by pediatric providers.

In conclusion, survival of pediatric patients on chronic dialysis has improved over two decades of dialysis registry data, particularly in children <1 year. Although improvements in several clinical performance measures, such as anemia and hypertension, have been noted in data from the most recent era, poor linear growth, black race, and young age continue to be poor predictors of survival and underscore the need for ongoing improvements in care. Cardiopulmonary disease continues to be the most common causes of death, highlighting again the ongoing importance of improved blood control and management of cardiovascular risk in these patients.

Compliance with ethical standards Local institutional review board approval was obtained at each center for data entry.

Conflict of interest None of the authors have a conflict of interest to resolve related to the current manuscript.

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