Editorial Commentary

Prediction of kidney failure in long-term survivors of childhood cancer—an opportunity for intervention in follow-up programs

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Outcome of childhood cancer treatment has improved tremendously in the last five decades and now reaches 80% in developed countries (1), while this was around 30% in the 1960's. This can be attributed to the advent of novel drugs and treatment modalities, improvement of supporting care but also to the knowledge gained by standardizing treatment in large co-operative studies. Treatment protocols were (and are still) systematically improved by comparing each modification to the current best standard.

It has become clear, however, that improved survival has led to long-term morbidity and mortality from late side-effects of treatment (2). About three out of four survivors face at least one or more late effect(s), of which 40% is severe, disabling or even life-threatening (2). Depending on the treatment given, this may involve almost any organ system such as heart, reproductive organs, thyroid, and central nervous system and has significant impact on patient well-being and mental health (3). Therefore, the co-operative treatment studies are followed up by a systematic recall of patients with use of (international) surveillance guidelines to search for (and treat if possible) late effects after cancer treatment in childhood.

Nephrotoxicity has long been recognized as a complication of radio- and chemotherapy (4). This is due to the high exposure (some 25% of the cardiac output is delivered to the kidneys per unit of time) and the high metabolic activity and energy demand of the tubular cells (5). Also, a number of highly toxic compounds such as platina derivatives and ifosfamide are actively reabsorbed by proximal tubular cells via organic anion transporters leading to direct damage of these cells (6). Hyperhydration schemes try to limit renal toxicity as much as possible. Irradiation of the kidney damages endothelial, glomerular and tubular cells. Chronic radiation nephropathy manifests after a latency period of years and is characterized by interstitial fibrosis, loss of nephron mass and sclerosis in renal vasculature (7). Wilms tumors—the most common kidney tumor in children—are treated by complete or partial nephrectomy which may lead to severely reduced nephron mass, in particular if both kidneys are involved (8). This may result in a vicious circle of hyperfiltration and progressive glomerular damage (9), in particular if the kidneys are exposed to additional stressors like obesity, hypertension, diabetes mellitus, high salt and protein intake and nephrotoxins (10).

Patients with neuroblastomas, bone tumors, soft tissue sarcomas and renal tumors are most prone to long-term kidney damage (11,12). Still, the most recent Cochrane review on late renal effects of cancer treatment in childhood dating from 2019 (4) concluded that the specific

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contribution of the different drugs and treatment modalities was elusive as these drugs are often administered in combination and most studies were too small to reach clear conclusions. Also, published series were too heterogenous to perform sound meta-analyses.

This has changed thanks to several recent papers, which analyzed large national patient cohorts in The Netherlands and the United States.

Out of 6,165 5-year survivors diagnosed between 1963 and 2001, the Dutch Childhood Cancer Survivor Study (DCCSS-LATER 2 study) launched in 2016, invited 4,735 survivors, 2,519 of whom decided to participate (13). Depending on tumor and treatment received potential late effects were sought for during this cross-sectional study. Since 2021, this has resulted in 23 papers addressing—among others—quality of life, fatigue and frailty, bone health, sexual function, cardiac function and oral health. The DCCSS-LATER 2 RENA study assessed late renal effects looking at glomerular (12) and tubular damage (11) and the prevalence and risk factors for hypertension after potentially nephrotoxic cancer treatment (14). For comparison with the general population the RENA study used data from 500 age- and sex-matched controls. 1,024 survivors participated in this cohort with a median age of 32.0 years.

Similar to the Dutch study, the St. Jude Lifetime Cohort Study (SJLIFE) for 5-year pediatric cancer survivors uses a retrospective cohort study design with prospective follow-up for patients treated at St. Jude Children's Research Hospital between 1962 and 2012 (15). Out of 7,471 survivors invited, 5,223 had completed a campus visit by March, 2020. The SJLIFE study also recruits age-, sex- and race-frequency matched controls without a history of malignancy from the same geographic area. The study has yielded numerous publications on the prevalence and burden of cancer treatment-related organ dysfunction and late health outcomes. A recent report on 2,753 survivors with a median age of 31.4 years addressed the prevalence of and risk factors for impaired kidney function at a median age of 31.4 years (16).

The Childhood Cancer Survivor Study (CCSS) recruited some 24,000 long-term childhood cancer survivors diagnosed between 1970 and 1999 from 31 participating centers in the United States and Canada and 5,000 of their siblings (17). Like the two other studies the CCSS addressed prevalence, risk factors for and disease burden of late effects of cancer treatment in childhood. The study group also prospectively evaluated screening strategies for secondary cancers and developed prediction models for adverse outcomes such as secondary neoplasms, heart failure, cardiovascular events, obesity and kidney failure.

All three study groups recently published data on long-term kidney damage in childhood cancer survivors. After a median follow-up of 23.2 years, an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 corresponding to chronic kidney disease (CKD) stage 3 to 5 was found in 2.1% of 2,753 survivors from the St. Jude cohort (16) and in 3.5% of 1,024 survivors (median follow-up 25.6 years) in the DCCSS LATER 2 RENA study (12). Of note, CKD 3 or higher was not observed in any of the matched controls in this study. Albuminuria was present in 15% of the cancer survivors and in only 1% of controls. In the CCSS cohort, Dieffenbach *et al.* reported a 35-year cumulative incidence of end-stage kidney disease (ESKD) of 1.7%, while this was only 0.2% in the sibling controls (18). This is in line with the DCCSS LATER 2 RENA cohort, where 1.1% had ESKD, while this was the case in only eight survivors (0.3%) in the St. Jude cohort.

These three independent cohorts clearly demonstrate the increased risk of developing CKD in long-term childhood cancer survivors and were sufficiently powered to assess risk factors for adverse kidney outcomes (*Table 1*). All three identified arterial hypertension, unilateral nephrectomy, abdominal irradiation, and ifosfamide treatment as risk factors for long-term kidney damage. Also, the risk increased consistently during follow-up. The DCCSS LATER 2 study demonstrated decreased kidney function already in the youngest cohort of survivors treated with nephrectomy, while kidney function remained comparable to controls in the oldest cohort without nephrectomy (*Figure 1*) (19). Anthracycline exposure ≥250 mg/m^2 was only associated with an increased risk ratio (RR) in the CCSS cohort, while dose dependent cisplatin toxicity was demonstrated in the DCCSS LATER2 and the SJLIFE study. Risk increased with older age at diagnosis in the Dutch cohort, while age below 10 years was a risk factor in the CCSS cohort. Of note, the presence of hypertension after nephrectomy increased the risk for kidney failure more than seven-fold in the CCSS cohort.

In a recent paper, Wu *et al.* used the CCSS cohort including 25,483 long-term childhood cancer survivors and 5,045 sibling controls to develop a prediction model for late ESKD (i.e., dialysis, transplantation, or kidney related death) diagnosed beyond the first 5 years from initial cancer diagnosis (20). Among the CCSS survivors, 204 had developed ESKD before the age of 40. The model was validated in two random samples of survivors taken

Table 1 Risk for CKD stage 3–5 in long-term childhood cancer survivors

Risk factors	Stage of CKD		
	CKD5	≥ CKD3	
	CCSS, RR (95% CI)	DCCSS LATER 2, OR (95% CI)	SJLIFE, OR (95% CI)
Nephrectomy (yes/no)	1.9 (1.0–3.4)	3.7 (2.1–6.4)	–
Hypertension (yes/no)	5.9[†] (3.3–10.5)	2.5[‡] (1.6–3.9)	8.4[§] (4.1–17.3)
Nephrectomy + hypertension	14.4 (7.1–29.4)	ns	–
Abdominal irradiation (yes/no)	–	1.8 (1.1–2.9)	–
Irradiation kidney dose			
5–15 Gy (per % kidney volume)	–	–	1.02 (1.0–1.2)
>15 Gy (yes/none)	4.0 (2.1–7.4)	–	–
>15 Gy + nephrectomy (yes/no)	–	–	3.6 (1.5–8.6)
<20 Gy (yes/none)	–	2.5 (1.2–5.1)	–
>30 Gy (yes/none)	–	2.1 (1.1–3.8)	–
Ifosfamide (yes/no)	2.4 (1.3–4.6)	2.9 (1.9–4.4)	–
Ifosfamide per g/m^2	–	–	1.04 (1.02–1.05)
Ifosfamide (12–42 g/m^2 *vs.* none)	–	3.2 (1.8–5.8)	–
Ifosfamide (>42 g/m^2 *vs.* none)	–	6.4 (3.4–12.2)	–
Ifosfamide + platinum agent	3.8 (1.8–8.0)	–	–
Cis-platinum per 100 mg/m^2	–	–	1.4 (1.2–1.6)
Cis-platinum (>500 mg/m^2 *vs.* none)	ns	7.2 (3.4–15.2)	–
Carboplatinum per 100 mg/m^2	–	ns	1.03 (1.0–1.06)
Follow-up per year	–	–	1.08 (1.04–1.1)
Follow-up (>30 *vs.* <20 years)	–	2.7 (1.6–4.8)	–

[†], any hypertension at 5 years follow-up; [‡], any hypertension or antihypertensive medication at last follow-up; [§], ≥ grade 2 at last follow-up. CKD, chronic kidney disease; CCSS, Childhood Cancer Survival Study; RR, risk ratio; CI, confidence interval; DCCSS LATER 2, Dutch Childhood Cancer Survival Study LATER 2; SJLIFE, St. Jude Lifetime Cohort Study; OR, odds ratio; ns, not significant.

from the SJLIFE cohort (n=2,490 out of 4,708; eight cases of ESKD) and the National Wilms Tumor Study (NWTS; n=396 out of 6,760 survivors, 91 cases of ESKD). The diagnosis of ESKD or death from kidney failure was confirmed by comparison with nationwide databases (Organ Procurement and Transplantation Network, the National Death Index and the United States Renal Data System). Because of potential overlap between the survivor registries, the authors made sure that each survivor was only included once.

Not surprisingly, most predictors for late kidney failure overlap with the earlier CCSS publication (18), i.e., nephrectomy, ifosfamide (binary and dose-dependent), high-dose anthracycline use, abdominal irradiation (binary and dose-dependent) and hypertension within 5 years of cancer diagnosis. The presence of genitourinary anomalies, which had not been significant in the previous publication [RR =1.7; 95% confidence interval (CI): 0.7–4.1] was significant in the new analysis (RR =2.7; 95% CI: 1.1–6.6), while new onset diabetes was no longer statistically significant. The last included predictor was black, non-Hispanic ethnicity.

Based on the height of the regression coefficient estimates compared to sibling controls integer risk scores were calculated which form the basis of the prediction model. Here, the simple model using binary (yes/no) predictors and the dose-specific model performed comparably both in

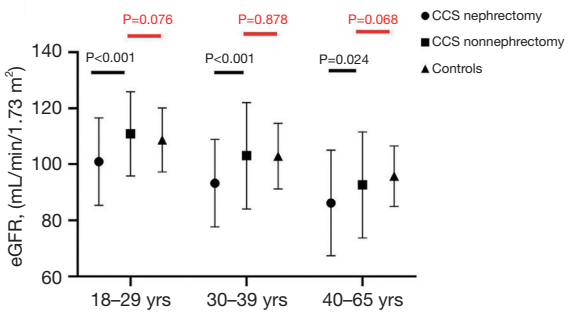

Figure 1 eGFR in long-term childhood cancer survivors who underwent nephrectomy compared to survivors without nephrectomy and to matched controls. Black numbers indicate the P values for analyses comparing CCS with nephrectomy to CCS without nephrectomy. Red numbers indicate the P values for analyses comparing CCS without nephrectomy to controls. Modified from Kooijmans *et al.* (19). eGFR, estimated glomerular filtration rate; CCS, childhood cancer survivors.

the training (C-statistic 0.68 *vs.* 0.69) and the two external validation cohorts: St. Jude 0.86 *vs.* 0.88 and NWTS 0.63 *vs.* 0.64. Therefore, the simple model is sufficiently accurate, which will facilitate implementation in clinical practice.

Cumulative risk scores were calculated to define clinically meaningful low-, medium- and high-risk groups. Survivors with a cumulative risk score below 3 (77% of the survivors) had a cumulative incidence of 0.6%. Still, even in this group, the relative risk was 3.2 times higher than in their sibling controls. The medium risk group (score 3–5) comprised 21% of the survivors and had an incidence of 2.3% (RR =10.8). In the high-risk group (1.7% of the survivors) the incidence was 9.4% and the risk for ESKD was 37.9 times higher than in the controls. The simple and the dose-adjusted models agreed well in classifying risk groups indicating that the model is a valid prediction tool.

The CCSS prediction model may prove highly useful to identify childhood cancer survivors who need more intensive follow-up. The prediction model is based on cancer treatment and patient characteristics during the first 5 years of follow-up and clearly demonstrates the negative effect of early-onset hypertension. Of note, the SJLIFE study identified late hypertension as the strongest risk factor for ESKD. Hypertension may go unnoticed as demonstrated in Wilms tumor survivors who had hypertension twice as often as children with a single kidney for non-tumoral reasons, but did not receive antihypertensive treatment (21). In the DCCSS LATER 2 RENA cohort, untreated hypertension diagnosed by office measurements was found in 12% (14). A pilot study of Ambulatory Blood Pressure Measurements (ABPM) in an increased risk subgroup identified masked hypertension (i.e., normal office blood pressure with hypertension on ABPM) in another 7.8%, and insufficient nocturnal blood pressure dipping was found in 20.8%.

The finding that genitourinary anomalies are a strong risk factor in Wu's model might reflect low-nephron endowment as part of congenital abnormalities of the kidney and urinary tract (CAKUT) (9,20). Low-nephron endowment is a known risk factor for arterial hypertension and may also be associated with low birthweight (9), which was not part of the set of predefined predictors. Also, syndromic forms of Wilms tumor such as Denys-Drash and Wilms tumor-Aniridia-Genitourinary anomalies-Retardation (WAGR) syndrome are often associated with genital anomalies. The underlying mutations lead to progressive loss of kidney function and renal prognosis is much worse than in patients with non-syndromic Wilms tumors (22).

In the current version of the CCSS prediction model acute kidney injury (AKI) during treatment of childhood cancer is not included as these data are very difficult to collect retrospectively. As a first attempt to analyze the effect of supportive treatment on long-term kidney outcomes, Green *et al.* included exposure to aminoglycosides, liposomal amphotericin and amphotericin B in their analysis. They found an increased relative risk of 1.02 per dose administered of liposomal amphotericin or amphotericin B (16). AKI may lead to CKD and ESKD as demonstrated in a large meta-analysis of 13 retrospective studies describing the follow-up of 1,472,743 older adults at risk for AKI (23). The hazard ratio to develop CKD was 8.8 for AKI *vs.* no AKI and 3.1 for reaching ESKD (*Table 2*). This risk was directly associated with the severity of AKI (2.0 for mild, 3.3 for moderate and 28.2 for severe AKI). Unpublished data from the Princess Máxima Center for pediatric oncology indicate that this holds true for children with cancer, too (24). This is in line with data from Park *et al.* who studied the incidence and impact of AKI in a cohort of 1,868 pediatric cancer patients; 52.6% of the studied cohort developed one or more episodes of AKI during the course of treatment. Having had more than four AKI episodes was an independent risk factor for impaired kidney function 5 years after cancer diagnosis (25). This underscores the importance of recognizing and documenting AKI during treatment of childhood cancer in order to optimize prediction models for chronic kidney damage in long-term survivors.

Table 2 Risk of developing CKD and ESKD after acute kidney injury

Outcomes	No. of studies	HR	95% CI	I^2 value
Outcome CKD stage				
AKI *vs.* no AKI	7	8.8	3–25.5	99%
Mild AKI *vs.* no AKI	2	2.0	1.4–2.8	74%
Moderate AKI *vs.* no AKI	3	3.3	1.7–6.2	63%
Severe AKI *vs.* no AKI	2	28.2	21.1–37.5	0%
Outcome ESKD				
AKI *vs.* no AKI	7	3.1	1.9–5.0	98%
Mild AKI *vs.* no AKI	4	2.3	1.7–3.3	84%
Moderate AKI *vs.* no AKI	3	5.0	2.6–9.8	88%
Severe AKI *vs.* no AKI	2	8.0	1.3–48.6	98%

I^2>75% indicates high heterogeneity between individual studies. The table was recreated based on Coca *et al.* (23). CKD, chronic kidney disease; ESKD, end-stage kidney disease; HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury.

In the meantime, the CCSS prediction model should be implemented to identify at risk patients at an earlier stage. This offers the opportunity to address potentially treatable risk factors such as obesity, high salt and protein intake, proteinuria, hypertension, acidosis, non-steroidal anti-inflammatory drug (NSAID) use and smoking (26).

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References

1. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5—a population-based study. Lancet Oncol 2014;15:35-47.
2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
3. Daniel LC, Wang M, Mulrooney DA, et al. Sleep, emotional distress, and physical health in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Psychooncology 2019;28:903-12.
4. Kooijmans EC, Bökenkamp A, Tjahjadi NS, et al. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst

Rev 2019;3:CD008944.
5. Ensergueix G, Pallet N, Joly D, et al. Ifosfamide nephrotoxicity in adult patients. Clin Kidney J 2020;13:660-5.
6. Hall AM, Trepiccione F, Unwin RJ. Drug toxicity in the proximal tubule: new models, methods and mechanisms. Pediatr Nephrol 2022;37:973-82.
7. Klaus R, Niyazi M, Lange-Sperandio B. Radiation-induced kidney toxicity: molecular and cellular pathogenesis. Radiat Oncol 2021;16:43.
8. van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, et al. Position paper: Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol 2017;14:743-52.
9. Luyckx VA, Brenner BM. Clinical consequences of developmental programming of low nephron number. Anat Rec (Hoboken) 2020;303:2613-31.
10. Tantisattamo E, Dafoe DC, Reddy UG, et al. Current Management of Patients With Acquired Solitary Kidney. Kidney Int Rep 2019;4:1205-18.
11. Kooijmans ECM, van der Pal HJH, Pluijm SMF, et al. Long-Term Tubular Dysfunction in Childhood Cancer Survivors; DCCSS-LATER 2 Renal Study. Cancers (Basel) 2022;14:2754.
12. Kooijmans ECM, van der Pal HJH, Pluijm SMF, et al. The Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 kidney analysis examined long-term glomerular dysfunction in childhood cancer survivors. Kidney Int 2022;102:1136-46.
13. Feijen EAM, Teepen JC, van Dulmen-den Broeder E, et al. Clinical evaluation of late outcomes in Dutch childhood cancer survivors: Methodology of the DCCSS LATER 2 study. Pediatr Blood Cancer 2023;70:e30212.
14. Kooijmans ECM, van der Pal HJH, Pluijm SMF, et al. Hypertension in long-term childhood cancer survivors after treatment with potentially nephrotoxic therapy; DCCSS-LATER 2: Renal study. Eur J Cancer 2022;172:287-99.
15. Howell CR, Bjornard KL, Ness KK, et al. Cohort Profile: The St. Jude Lifetime Cohort Study (SJLIFE) for paediatric cancer survivors. Int J Epidemiol 2021;50:39-49.
16. Green DM, Wang M, Krasin M, et al. Kidney Function after Treatment for Childhood Cancer: A Report from the St. Jude Lifetime Cohort Study. J Am Soc Nephrol 2021;32:983-93.
17. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol 2009;27:2308-18.
18. Dieffenbach BV, Liu Q, Murphy AJ, et al. Late-onset kidney failure in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer 2021;155:216-26.
19. Kooijmans ECM, van der Pal HJH, Veening MA, et al. Kidney Int 2023;103:227-8.
20. Wu NL, Chen Y, Dieffenbach BV, et al. Development and Validation of a Prediction Model for Kidney Failure in Long-Term Survivors of Childhood Cancer. J Clin Oncol 2023;41:2258-68.
21. Mavinkurve-Groothuis AM, van de Kracht F, Westland R, et al. Long-term follow-up of blood pressure and glomerular filtration rate in patients with a solitary functioning kidney: a comparison between Wilms tumor survivors and nephrectomy for other reasons. Pediatr Nephrol 2016;31:435-41.
22. Breslow NE, Collins AJ, Ritchey ML, et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol 2005;174:1972-5.
23. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81:442-8.
24. Raymakers-Janssen PAMA. Excess of nephrotoxicity in the full first 5 years cohort of childhood cancer patients treated in the Princess Maxima Center, results of a multistate model. Valencia, Spain: 4th Annual Meeting of the European Society for Paediatric Oncology; 2023.
25. Park PG, Hong CR, Kang E, et al. Acute Kidney Injury in Pediatric Cancer Patients. J Pediatr 2019;208:243-250.e3.
26. Hannan M, Ansari S, Meza N, et al. Risk Factors for CKD Progression: Overview of Findings from the CRIC Study. Clin J Am Soc Nephrol 2021;16:648-59.

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