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The Netherlands

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Chronic kidney disease ten years after pediatric allogeneic hematopoietic stem cell transplantation

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Gertjan Lugthart[1,2], Carlijn C.E. Jordans[1], Anne P.J. de Pagter[1], Dorine Bresters[1,3], Cornelia M. Jol-van der Zijde[1], Joell E. Bense[1], Roos W.G. van Rooij-Kouwenhoven[1], Ram N. Sukhai[1], Marloes Louwerens[4], Eiske M. Dorresteijn[1,2,5] and Arjan C. Lankester[1,5]

[1]*Willem-Alexander Children's Hospital, Department of Pediatrics, Leiden University Medical Center, Leiden, the Netherlands;* [2]*Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands;* [3]*Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands; and* [4]*Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands*

Chronic kidney disease (CKD) is an important sequela of hematopoietic stem cell transplantation (HSCT), but data regarding CKD after pediatric HSCT are limited. In this single center cohort study, we evaluated the estimated glomerular filtration rate (eGFR) dynamics, proteinuria and hypertension in the first decade after HSCT and assessed risk factors for CKD in 216 pediatric HSCT survivors, transplanted 2002-2012. The eGFR decreased from a median of 148 to 116 ml/min/1.73 m^2 between pre-HSCT to ten years post-HSCT. CKD (KDIGO stages G2 or A2 or more; eGFR under 90 ml/min/1.73m^2 and/or albuminuria) occurred in 17% of patients. In multivariate analysis, severe prolonged stage 2 or more acute kidney injury (AKI), with an eGFR under 60ml/min/1.73m^2 and duration of 28 days or more, was the main risk factor for CKD (hazard ratio 9.5, 95% confidence interval 3.4-27). Stage 2 or more AKI with an eGFR of 60ml/min/1.73m^2 or more and KDIGO stage 2 or more AKI with eGFR under 60ml/min/1.73m^2 but recovery within 28 days were not associated with CKD. Furthermore, hematological malignancy as HSCT indication was an independent risk factor for CKD. One third of patients had both CKD criteria, one third had isolated eGFR reduction and one third only had albuminuria. Hypertension occurred in 27% of patients with CKD compared to 4.4% of patients without. Tubular proteinuria was present in 7% of a subgroup of 71 patients with available β2-microglobulinuria. Thus, a significant proportion of pediatric HSCT recipients developed CKD within ten years. Our data stress the importance of structural long-term monitoring of eGFR, urine and blood pressure after HSCT to identify patients with incipient CKD who can benefit from nephroprotective interventions.

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KEYWORDS: acute kidney injury; albuminuria; cancer; chronic kidney disease; cytomegalovirus; hypertension; nephrotoxicity; pediatric nephrology; proteinuria; transplantation

Correspondence: *Gertjan Lugthart, Department of Pediatrics, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, the Netherlands. E-mail: g.lugthart@lumc.nl*

[5]EMD and ACL contributed equally to this article.

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Allogeneic hematopoietic stem cell transplantation (HSCT) is applied as a curative treatment for patients with hematological malignancies, bone marrow failure syndromes, hemoglobinopathies, inborn errors of immunity, and inborn errors of metabolism.[1] Over the last decades, survival rates following (pediatric) HSCT have greatly improved, and protocols have been adapted to reduce the long-term sequela of HSCT. In many HSCT recipients, preexistent subclinical kidney damage is present because of medication, chemotherapy, or complications of primary disease.[2,3] Nephrotoxic conditioning regimens before HSCT, as well as various nephrotoxic drugs that are frequently used in the period after HSCT, bear the risk of both acute kidney injury (AKI) and chronic kidney disease (CKD).[3] In adults, CKD is reported in 5% to 30% of long-term HSCT survivors, and frequently reported risk factors are the occurrence of AKI, older age, cyclosporine A use, total body irradiation (TBI), and chronic graft-versus-host disease.[4–11] The reported incidence of CKD after pediatric HSCT varies between 0% and 44%.[12–29] This is comparable to the reported incidence of CKD after adult HSCT. However, in studies that included both pediatric and adult HSCT recipients, the incidence of CKD was significantly lower in children.[11,20,26] Few studies systematically assessed the risk factors for CKD in pediatric HSCT recipients or were large enough to draw firm conclusions.[13,16,21] Data on proteinuria, tubular kidney function, and hypertension after pediatric HSCT are scarce as well. In the current study, we evaluated risk factors for CKD and assessed estimated glomerular filtration rate (eGFR) dynamics, albuminuria, β2-microglobulinuria, and hypertension in a large single-center cohort of pediatric HSCT recipients during 10 years of follow-up.

METHODS

Patients

Between January 2003 and December 2012, 320 children received an allogeneic HSCT in the Leiden University Medical Center as a treatment for hematological malignancy or severe nonmalignant diseases (bone marrow failure syndrome, hemoglobinopathy, or

inborn error of immunity). Transplantations were performed according to European Society for Blood and Marrow Transplantation guidelines. Peripheral blood samples and urine samples were routinely obtained. Medical records were analyzed retrospectively. The study protocol was evaluated and approved by the institutional review board (G20.049).

A flowchart of patient inclusion is shown in Figure 1. Only patients surviving >1 year after HSCT were included in this study because of (i) time required to establish CKD and (ii) evaluated risk factors occurring during the first year after HSCT. A total of 216 patients survived the first year after HSCT without relapse, retransplantation, or death. A total of 155 patients reached the 10-year post-HSCT evaluation point. A total of 61 patients were censored at a median of 3.1 years (range, 1.0–5.5 years) after HSCT because of second transplantation (n = 6), relapse of malignancy (n = 9), or death (n = 11). A total of 18 patients were lost to follow-up. Because kidney function was evaluated every 3 to 5 years, the 10-year post-HSCT nephrologic evaluation was not yet performed at closure of this study in 17 patients.

Supportive care

During conditioning with any of the drugs busulfan, etoposide, melphalan, fludarabine, treosulfan, and thiotepa, patients received oral and i.v. hydration (2 L/m^2). During cyclophosphamide conditioning, patients received hyperhydration (3 L/m^2) and 2-mercaptoethane sulfonate sodium. During cidofovir treatment, patients received hyperhydration (3 L/m^2) and oral probenecid for nephroprotection.[29] Therapeutic drug monitoring was applied for busulfan, cyclosporine A, gentamycin, tacrolimus, and vancomycin. In patients with a reduced kidney function, dose reduction of nephrotoxic drugs was applied in line with institutional recommendations.

Monitoring of kidney function

Routinely measured serum creatinine (SCr) values were used to monitor the glomerular function before the start of conditioning therapy (pre-HSCT), at 3 and 6 months and 1, 3, and 10 years after HSCT, or at latest stable follow-up before censoring. Urine analysis was performed, measuring creatinine, albumin, and β2-microglobulin in a portion of urine. Blood pressure was measured using automatic oscillometric blood pressure monitors at every hospital visit. Kidney function was evaluated every 3 to 5 years, and the moment closest to 10 years after HSCT was used for 10-year evaluation.

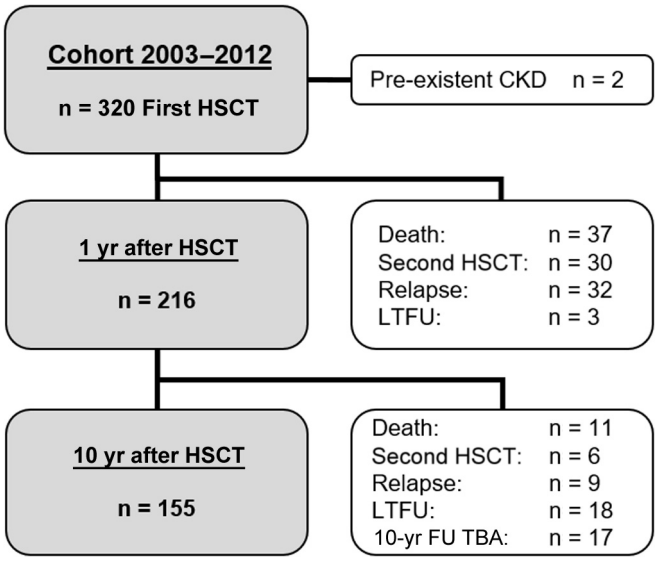

Figure 1 | Patient inclusion. Flowchart of patient inclusion. CKD, chronic kidney disease; FU TBA, follow-up to be assessed (10 years post–hematopoietic stem cell transplantation evaluation not reached); HSCT, hematopoietic stem cell transplantation; LTFU, lost to follow-up.

Definition of CKD

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were used for the classification of CKD.[30] CKD was defined as an eGFR of <90 ml/min per 1.73 m^2 at ≥2 measurements over a period of at least 3 months (KDIGO stage G2 or lower) and/or albuminuria (KDIGO stage A2). For patients aged <18 years, the eGFR was calculated using the updated Schwartz formula with modification of the K for pubertal boys [(K × length)/SCr] with K = 36.5 (girls and boys aged 0–12 years) or K = 40 (boys aged 12–18 years), length in cm, and SCr in μmol/L.[31–33] For adults, the CKD Epidemiology Collaboration formula was used [41 × min(SCr/K, 1)$^{\alpha}$ × max(SCr/K, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if Black)] with K = 61.9 (females) or K = 79.6 (males) and α = –0.329 (females) or –0.411 (males) and SCr in μmol/L.[34] Albuminuria was defined as an albumin-to-creatinine ratio of >3 mg/mmol in a portion of urine.[30] For tubular proteinuria, β2-microglobulin–to–creatinine ratio >50 μg/mmol was used as cutoff value. Hypertension was defined as a diastolic or systolic blood pressure >95th percentile for sex, age, and length at ≥2 consecutive hospital visits, or the use of antihypertensive medication.

Evaluated risk factors

For the univariate and multivariate analysis of risk factors for the development of CKD after HSCT, we evaluated the impact of baseline patient characteristics (age, sex, and primary disease category) and HSCT characteristics (donor type, graft source and manipulation, serotherapy, chemotherapeutic agents, and TBI). The influence of the following major post-transplant events was evaluated: acute and chronic graft-versus-host disease (≥grade/score 2) and cytomegalovirus, Epstein-Barr virus, or adenovirus reactivation (viral load ≥10^3 copies/ml at 2 consecutive measurements) and BK virus hemorrhagic cystitis (macroscopic hematuria with positive urine polymerase chain reaction). Furthermore, the impact of use of nephrotoxic drugs (listed in Table 1) and occurrence of veno-occlusive disease and transplant-related thrombotic microangiopathy were evaluated. Finally, the effect of AKI within the first year after HSCT on the development of CKD was evaluated. KDIGO definitions for AKI were used.[35] No data on urinary output were available. Mild KDIGO stage 1 AKI occurred in almost all patients and was therefore not evaluated. KDIGO AKI stages 2 and 3 are defined as a 2-fold and 3-fold, respectively, increase of SCr compared with baseline within the period of 1 week.[35] Patients with stage ≥2 AKI were further subdivided in 3 groups based on severity of AKI: AKI with lowest eGFR ≥60 ml/min per 1.73 m2, irrespective of duration; AKI with lowest eGFR <60 ml/min per 1.73 m2, which recovered within 28 days to an SCr value <1.5 times baseline; and AKI with lowest eGFR <60 ml/min per 1.73 m2 and duration ≥28 days.

Statistical analysis

For eGFR dynamics, Wilcoxon matched-pairs signed rank test was performed to compare different time points after HSCT. A Cox proportional hazards model was applied to calculate the hazard ratio (HR) and 95% confidence interval of potential risk factors on the

Table 1 | Patient Characteristics (n = 216)

Characteristic	No.	%
Age at transplantation, yr		
0–6	87	40.2
6–12	65	30.1
12–19	64	29.6
Sex		
Female	80	37.0
Male	136	63.0
Primary diagnosis		
Nonmalignant diseases	120	55.6
Inborn error of immunity	40	18.5
Bone marrow failure syndrome	44	20.4
Hemoglobinopathy	36	16.7
Hematological malignancy	96	44.4
Acute lymphoblastic leukemia	51	23.6
Acute myeloblastic leukemia	18	8.3
Other hematological malignancy	27	12.5
Donor type		
Identical related donor	70	32.0
Matched unrelated donor	128	59.3
Mismatched related donor	18	8.3
Graft source		
Bone marrow	164	75.9
Peripheral blood stem cells	35	16.2
Cord blood	17	7.9
T-cell depletion of the graft	18	8.3
Serotherapy		
Anti-thymocyte globulin	143	66.2
Alemtuzumab	30	13.9
No serotherapy	51	23.6
Conditioning regimen		
Busulfan-based	99	45.8
Treosulfan-based	27	12.5
Total body irradiation–based	62	28.7
Other regimens	28	13.0
Graft-versus-host disease		
Acute (≥ grade 2)	33	15.3
Chronic (≥ score 2)	13	6.0
Viral infections		
Cytomegalovirus	47	21.8
Epstein-Barr virus	34	15.7
Human adenovirus	20	9.3
BK virus cystitis	35	16.2
Other major complications		
Veno-occlusive disease	14	6.5
Thrombotic microangiopathy	0	0
AKI, KDIGO definition		
No AKI	121	56.0
Stage 2 AKI	63	29.2
Stage 3 AKI	32	14.8
AKI, KDIGO + lowest eGFR and duration[a]		
No AKI	121	56.0
Stage ≥2 AKI, eGFR ≥60 ml/min per 1.73 m^2, <28 d or ≥28 d	55	25.5
Stage ≥2 AKI, eGFR <60 ml/min per 1.73 m^2, <28 d	26	12.0
Stage ≥2 AKI, eGFR <60 ml/min per 1.73 m^2, ≥28 d	14	6.5
Nephrotoxic medication		
Amphotericin B	7	3.2
Cyclosporine A	207	96.8
Cidofovir	25	11.6
Ganciclovir	20	9.3
Foscarnet	31	14.4
Furosemide[b]	134	62.0
Gentamycin	8	3.7
Tacrolimus	8	3.7
Vancomycin	198	91.7

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.
[a]Patients with KDIGO stage ≥2 AKI were subdivided based on the lowest eGFR and duration: AKI with the lowest eGFR ≥60 ml/min per 1.73 m^2; AKI with the lowest eGFR <60 ml/min per 1.73 m^2 that recovered within 28 days; and AKI with the lowest eGFR <60 ml/min per 1.73 m^2 and duration ≥28 days.
[b]Only structural (>5 days) furosemide included.
Patient characteristics, transplantation variables, and post-transplant events and medication in 216 pediatric hematopoietic stem cell transplantation (HSCT) recipients who survived >1 year after HSCT without relapse or retransplantation.

occurrence of CKD after HSCT. All potential risk factors were included in a multivariate logistic regression analysis using backward stepwise elimination. In the adjusted model, hypertension (n = 14) and diabetes mellitus (n = 1) were added as risk factor in the evaluation. Patients were censored at the latest available data point in steady-state conditions, at least 1 month before the censoring events of death, retransplantation, or relapse, or at the latest visit before loss of follow-up. Parameters were tested for the proportional hazards assumption using the graphical approach (log minus log survival plots). $P < 0.05$ was considered statistically significant. Multinomial parameters were only considered significant if the Wald test had a $P < 0.05$ as well. Analysis was performed using SPSS Statistics 25 (IBM SPSS Inc). GraphPad Prism (version 6.05; GraphPad Software) was used to construct figures.

RESULTS

Patient characteristics

Between 2003 and 2012, 320 children received an allogeneic HSCT in our center. Two patients were excluded because of preexistent CKD. A total of 216 patients survived >1 year without relapse of malignancy or retransplantation and were included in this study (Figure 1). Detailed patient characteristics are listed in Table 1. At the time of HSCT, the median age was 7.8 years (range, 3 months–19 years). Median follow-up was 8.1 years (range, 1.0–14 years). Indications for HSCT were hematological malignancy (44%) or severe nonmalignant diseases (56%): bone marrow failure syndrome (20%), hemoglobinopathy (17%), and inborn error of immunity (19%). Patients received TBI-based conditioning (29%) or chemotherapy-based conditioning (70%). In the first year after HSCT, all patients received at least one of the nephrotoxic drugs listed in Table 1. A total of 84 patients had a significant reactivation of cytomegalovirus, Epstein-Barr virus, or human adenovirus. A total of 35 patients developed a hemorrhagic BK cystitis. In the first year after HSCT, KDIGO stage 2 and 3 AKI occurred in 63 and 32 patients, respectively. Of patients with stage ≥2 AKI, 55 (25.5%) had AKI with eGFR ≥60 ml/min per 1.73 m^2, 26 (12%) had AKI with eGFR <60 ml/min per 1.73 m^2 that recovered within 28 days, and 14 (6.5%) had prolonged severe AKI with eGFR <60 ml/min per 1.73 m^2 and duration ≥28 days. In patients with

prolonged severe AKI, this was associated with fluid overload treated with diuretics (n = 6), nephrotoxic antiviral medication (cidofovir [n = 3] and/or foscarnet [n = 6]), veno-occlusive disease (n = 2), hemorrhagic BK virus cystitis with oliguria (n = 1), or prerenal with increased cyclosporine A blood levels (n = 3). In 4 cases, a combination of these factors was recognized (Supplementary Table S1). In 1 case, AKI occurred 6 months after HSCT without provoking factors; renal biopsy showed radiation nephropathy.

eGFR dynamics

Before HSCT, the median eGFR was 148 ml/min per 1.73 m^2 (range, 81–311 ml/min per 1.73 m^2; Figure 2). At 3 months after HSCT, the median eGFR decreased to 128 ml/min per 1.73 m^2 (range, 43–244 ml/min per 1.73 m^2; $P < 0.0001$). In 21 of 28 patients (75%) with an eGFR <90 ml/min per 1.73 m^2 at 3 months after HSCT, this reduction was transient and the eGFR recovered during the first year after HSCT. At group level, the eGFR remained stable between 3 and 12 months after HSCT. After the first year, the eGFR decreased from a median of 131 ml/min per 1.73 m^2 to a median of 126 ml/min per 1.73 m^2 at 3 years after HSCT and a median of 116 ml/min per 1.73 m^2 (range, <10–322 ml/min per 1.73 m^2) at 10 years after HSCT (1 vs. 3 years after HSCT: $P = 0.007$; 1 vs. 10 years after HSCT: $P < 0001$; and 3 vs. 10 years after HSCT: $P < 0.0001$; Figure 2).

Incidence, timing, and risk factors for CKD

From the 216 children who survived >1 year after HSCT, 37 (17.1%) developed CKD during follow-up (median, 8.1 years; range, 1.0–14 years). CKD was defined as either an eGFR <90 ml/min per 1.73 m^2 (KDIGO stage ≥G2) or albuminuria (KDIGO stage ≥A2).[30] The vast majority of CKD patients developed CKD >5 years after HSCT (Figure 3a). Median age of onset of CKD was 19 years (range, 4.0–29 years). Only 6 of 37 CKD patients were prepubertal at the moment they developed CKD.

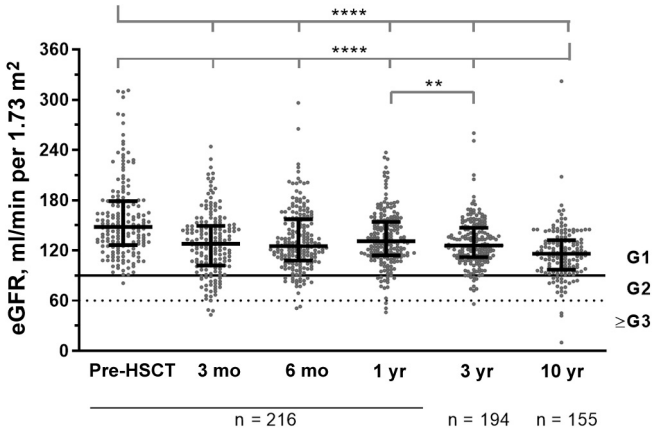

Figure 2 | Estimated glomerular filtration rate (eGFR) dynamics after hematopoietic stem cell transplantation (HSCT). Dynamics of the glomerular kidney function in 216 pediatric HSCT recipients. Shown is the eGFR preconditioning (pre-HSCT), and the eGFR during longitudinal follow-up. Horizontal lines: cutoff values for chronic kidney disease Kidney Disease: Improving Global Outcomes (KDIGO) ≥ stage G2 (90 ml/min per 1.73 m^2) and KDIGO ≥ stage G3 (60 ml/min per 1.73 m^2). Bars = median and interquartile range. Statistics: $^{**}P < 0.01$, $^{****}P < 0.0001$.

We evaluated the impact of baseline patient characteristics, HSCT parameters, post-transplant events, and use of nephrotoxic medication on the development of CKD. The potential risk factors included in this analysis are listed in Table 2, which also shows their univariate and multivariate HRs for CKD. Classification of AKI based on KDIGO stages 2 and 3 AKI was not discriminative to identify patients at risk for CKD (Table 2). Further categorization of patients with KDIGO stage ≥2 AKI, based on the lowest eGFR and duration of AKI, revealed that prolonged severe AKI with eGFR <60 ml/min per 1.73 m^2 and duration ≥28 days had a strongly increased HR for CKD. In contrast, AKI with eGFR ≥60 ml/min per 1.73 m^2 and AKI with eGFR <60 ml/min per 1.73 m^2 that recovered within 28 days were not associated with the development of CKD. The use of cyclosporine A as graft-versus-host disease prophylaxis had a decreased HR for CKD (Table 2).

In multivariate analysis, patients who went through AKI with eGFR <60 ml/min per 1.73 m^2 and duration ≥28 days in the first year after HSCT had an increased risk of CKD (HR, 9.5; 95% confidence interval, 3.4–27; Table 2 and Figure 3b). Patients with hematological malignancy as HSCT indication had an increased HR for the development of CKD (HR, 3.5; 95% confidence interval, 1.4–8.6; Table 2 and Figure 3c). In contrast, a decreased HR for CKD was observed in patients who received cyclosporine A as graft-versus-host disease prophylaxis (HR, 0.2; 95% confidence interval, 0.1–0.3). As diabetes mellitus and hypertension are associated with proteinuria, correction for diabetes mellitus (n = 1) and hypertension (n = 14) was performed, which did not affect the outcome of the multivariate analysis (Supplementary Table S2).

The incidence of CKD was comparable between patients with different hematological malignancies. Within the more heterogeneous group of patients with nonmalignant diseases, patients transplanted for inborn errors of immunity had a lower incidence of CKD (5%) compared with patients with hemoglobinopathies (14%) or bone marrow failure syndromes (23%; $P = 0.067$; Supplementary Figure S1).

Comprehensive evaluation of kidney function 10 years after HSCT

Finally, we evaluated kidney function of the long-term HSCT survivors in more detail. A total of 155 patients survived without relapse or retransplantation and were available for follow-up at 10 years after HSCT (range, 7.5–14 years; median, 9.7 years; Figure 1). CKD, defined as KDIGO stage ≥G2 or ≥A2, was present in 33 of 155 patients (21.3%).

Twenty-one patients (13.5%) had an eGFR <90 ml/min per 1.73 m^2 at 10 years after HSCT. Three patients (2%) had an eGFR <60 ml/min per 1.73 m^2. One of them received renal replacement therapy and died from CKD while listed for

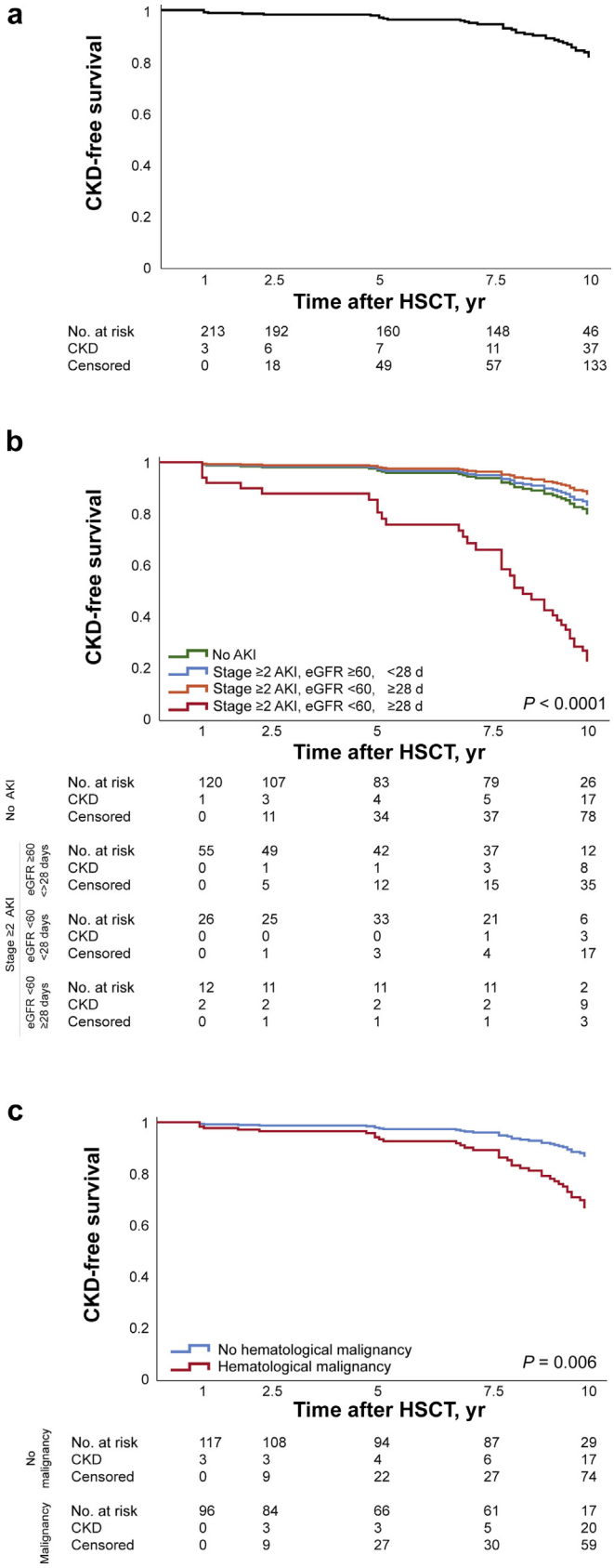

Figure 3 | Chronic kidney disease (CKD)–free survival after hematopoietic stem cell transplantation (HSCT). (**a**) Disease-free survival curve of CKD after pediatric HSCT. (Continued)

renal transplant. Early after HSCT, this patient went through a disseminated adenovirus infection and BK virus cystitis, treated with systemic cidofovir. This patient did not encounter AKI but developed obstructive uropathy and progressive CKD in the years after HSCT.

Three patterns of eGFR dynamics could be distinguished in patients with CKD at 10 years after HSCT (Figure 4a). Of 21 patients, 5 had a >30% reduction of eGFR within the first months after HSCT, which did not recover thereafter. Eight patients had a >30% eGFR reduction within the first months after HSCT, which recovered at 1 to 3 years after HSCT, but then decreased in the following years. In another 8 patients, eGFR reduction occurred after the first year post-HSCT (Figure 4a).

Urine samples were available in 132 of 155 long-term HSCT survivors. A total of 18 patients (13.6%) had albuminuria. Tubular protein loss was evaluated in a subgroup of 71 patients. β2-Microglobulinuria was observed in 5 patients (7%). Two patients with CKD had biochemical signs of tubular kidney disease and required supplementation of bicarbonate, magnesium, and/or phosphate at 10 years after HSCT.

Ten years after HSCT, blood pressure measurements were available for analysis in 146 of 155 patients. In total, 14 patients (9%) had hypertension. Three patients had both systolic and diastolic hypertension, 1 patient had isolated systolic hypertension, and 5 patients had isolated diastolic hypertension. Five patients were using antihypertensive medication. The incidence of hypertension was 6 times higher in patients with CKD than in patients without CKD; 9 of 33 CKD patients (27%) had hypertension compared with 5 of 113 non-CKD patients (4.4%; $P < 0.0001$; Figure 4b).

DISCUSSION

We performed longitudinal follow-up of kidney function in a large cohort of 216 pediatric HSCT recipients. One out of 6 patients (17%) developed CKD within 10 years after HSCT. One-third of the CKD patients had both an eGFR <90 ml/min per 1.73 m^2 as well as albuminuria, one-third had isolated eGFR reduction, and one-third only had albuminuria. Independent risk factors for CKD were hematological malignancy and prolonged severe AKI with eGFR <60 ml/min

Figure 3 | (Continued) (**b**) Covariate-adjusted survival curves from the multivariate Cox proportional hazards model for acute kidney injury (AKI). Patients with Kidney Disease: Improving Global Outcomes (KDIGO) stage ≥2 AKI were subdivided based on lowest estimated glomerular filtration rate (eGFR) and duration: AKI with the lowest eGFR ≥60 ml/min per 1.73 m^2; AKI with the lowest eGFR <60 ml/min per 1.73 m^2 that recovered within 28 days; and AKI with the lowest eGFR <60 ml/min per 1.73 m^2 and duration ≥28 days. (**c**) Covariate-adjusted survival curves from the multivariate Cox proportional hazards model for hematological malignancy. CKD was defined as KDIGO stage ≥G2 or ≥A2. For graphical reasons, events >10 years after HSCT were plotted at 10 years after HSCT, and patients with follow-up >7.5 years were censored at 10 years after HSCT. Statistical analysis was performed with the actual time of event or censoring.

Table 2 | HRs from Cox proportional hazards model

Characteristic	CKD, no.		Univariate Cox regression			Multivariate Cox regression		
	No (n = 179)	Yes (n = 37)	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Age at transplantation, yr					0.065			
0–6	79	8	1.0					
6–12	54	11	2.0	(0.8–4.9)	0.140			
12–19	46	18	2.7	(1.2–6.2)	0.019			
Sex								
Female	66	14	1.0					
Male	113	23	0.8	(0.4–1.6)	0.590			
Primary diagnosis								
Nonmalignant diseases	103	17	1.0					
Hematological malignancy	76	20	1.5	(0.8–2.9)	0.218	3.5	(1.4–8.6)	0.006
Donor type					0.386			
Identical related donor	61	9	1.0					
Matched unrelated donor	103	25	1.7	(0.8–3.7)	0.172			
Mismatched related donor	15	3	1.3	(0.4–4.9)	0.676			
Graft source					0.515			
Bone marrow	136	28	1.0					
Peripheral blood stem cells	27	8	1.3	(0.6–2.7)	0.569			
Cord blood	16	1	0.4	(0.1–2.8)	0.343			
T-cell depletion of the graft	15	3	0.9	(0.3–3.0)	0.905			
Serotherapy								
Anti-thymocyte globulin	121	22	0.9	(0.5–1.8)	0.846			
Alemtuzumab	19	11	2.0	(1.0–4.1)	0.055			
Conditioning regimen					0.342			
Busulfan-based	87	12	1.0					
Treosulfan-based	23	4	1.3	(0.4–3.9)	0.685			
Total body irradiation–based	48	14	1.5	(0.7–3.3)	0.305			
Other regimens	21	7	2.4	(0.9–6.0)	0.073			
Graft-versus-host disease								
Acute (≥ grade 2)	27	6	1.2	(0.5–2.9)	0.691			
Chronic (≥ score 2)	9	4	2.0	(0.7–5.8)	0.175			
Viral infections								
Cytomegalovirus	36	11	1.6	(0.8–3.3)	0.169			
Epstein-Barr virus	26	8	1.5	(0.7–3.4)	0.278			
Human adenovirus	16	4	1.5	(0.5–4.1)	0.481			
BK virus cystitis	27	8	1.6	(0.7–3.5)	0.235			
Other major complications								
Veno-occlusive disease	11	3	1.1	(0.3–3.7)	0.840			
Thrombotic microangiopathy	0	0			NA			
AKI, KDIGO definition					0.707			
No AKI	104	17	1.0					
Stage 2 AKI	50	13	1.3	(0.7–2.7)	0.640			
Stage 3 AKI	25	7	1.3	(0.5–3.0)	0.251			
AKI, KDIGO + lowest eGFR and duration[a]					0.001			<0.0001
No AKI	104	17	1.0			1.0		
Stage ≥2 AKI, eGFR ≥60 ml/min per 1.73 m^2, <28 d or ≥28 d	47	8	0.9	(0.4–2.1)	0.854	0.8	(0.3–1.9)	0.608
Stage ≥2 AKI, eGFR <60 ml/min per 1.73 m^2, <28 d	23	3	0.7	(0.2–2.5)	0.569	0.8	(0.2–2.9)	0.711
Stage ≥2 AKI, eGFR <60 ml/min per 1.73 m^2, ≥28 d	5	9	4.4	(2.0–10.0)	<0.0001	9.5	(3.4–26.9)	<0.0001
Nephrotoxic medication								
Amphotericin B	7	0	NA		NA			
Cyclosporine A	174	33	0.2	(0.1–0.6)	0.005	0.2	(0.1–0.3)	0.005
Cidofovir	19	6	1.6	(0.7–3.9)	0.274			
Ganciclovir	15	5	1.6	(0.6–4.1)	0.332			
Foscarnet	23	8	1.7	(0.8–3.6)	0.205			
Furosemide[b]	116	18	0.7	(0.4–1.3)	0.266			
Gentamycin	6	2	1.2	(0.3–4.8)	0.850			
Tacrolimus	5	3	3.1	(1.0–10.3)	0.059			
Vancomycin	164	34	1.0	(0.3–3.3)	0.981			

AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not analyzed.

[a]Patients with KDIGO stage ≥2 AKI were subdivided based on lowest eGFR and duration: AKI with the lowest eGFR ≥60 ml/min per 1.73 m^2; AKI with the lowest eGFR <60 ml/min per 1.73 m^2 that recovered within 28 days; and AKI with the lowest eGFR <60 ml/min per 1.73 m^2 and duration ≥28 days.

[b]Only structural (>5 days) furosemide included.

Risk factors for CKD evaluated in univariate and multivariate Cox proportional hazards model. CKD was defined as KDIGO stage ≥G2 or ≥A2. HR, 95% CI, and *P* value are shown. For multinomial parameters, the *P* value from Wald test is shown as well. A total of 216 survivors of hematopoietic stem cell transplantation were included, of whom 37 developed CKD and 133 were censored. All listed parameters were included in a stepwise backward elimination multivariate Cox proportional hazards model. Only parameters that were retained in the multivariate model are shown in the multivariate table.

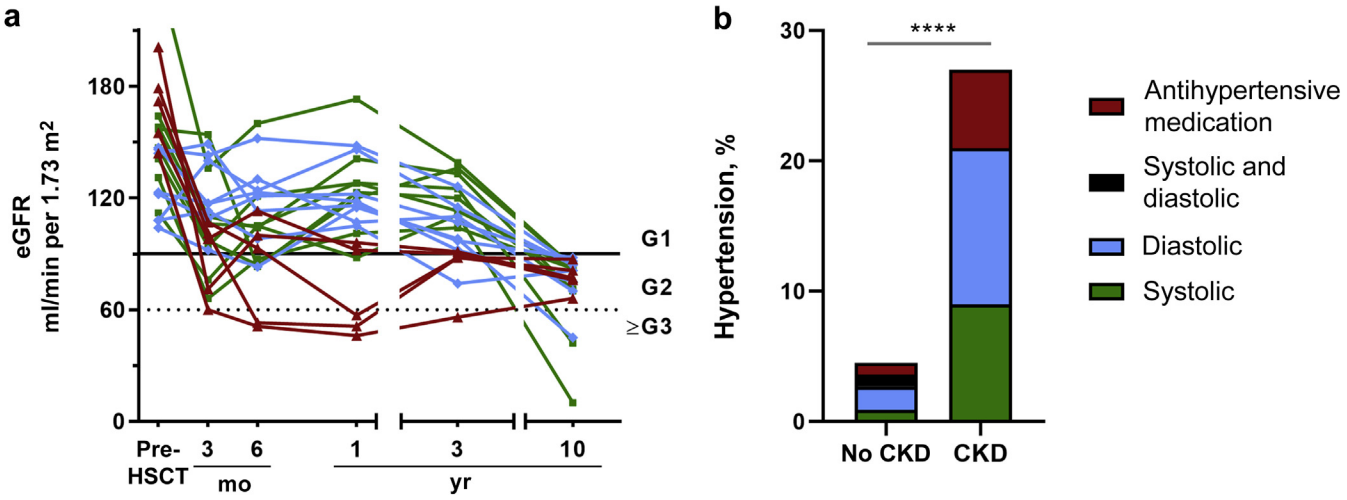

Figure 4| Estimated glomerular filtration rate (eGFR) dynamics of chronic kidney disease (CKD) patients and incidence of hypertension. (**a**) Dynamics of eGFR in 21 patients with CKD Kidney Disease: Improving Global Outcomes (KDIGO) ≥ stage G2 at 10 years after hematopoietic stem cell transplantation (HSCT). Red triangles: rapid eGFR reduction without recovery. Green squares: rapid eGFR reduction with initial recovery but subsequent eGFR reduction. Blue diamonds: stable eGFR in first year, but subsequent eGFR reduction. Horizontal lines: cutoff values for CKD KDIGO stage ≥G2 (90 ml/min per 1.73 m^2) and KDIGO stage ≥G3 (60 ml/min per 1.73 m^2). (**b**) Incidence of hypertension in 146 HSCT recipients at 10 years after HSCT: 123 patients without CKD and 33 patients with CKD. Bars = patients using antihypertensive medication (red), patients with systolic hypertension (green), patients with diastolic hypertension (blue), or patients with both systolic and diastolic hypertension (black). Statistics: ****$P < 0.0001$.

per 1.73 m^2 and duration ≥28 days. In contrast, AKI with eGFR ≥60 ml/min per 1.73 m^2 and AKI with eGFR <60 ml/min per 1.73 m^2 that recovered within 28 days were not associated with the development of CKD.

We were able to monitor the kidney function of HSCT recipients for 10 years after HSCT and into adulthood, and used KDIGO criteria to uniformly grade the severity of CKD.[30] This long-term follow-up is crucial, because many patients developed CKD >5 years after HSCT and after they had reached the pubertal age. The incidence of CKD in our cohort was higher than in most other studies describing CKD in pediatric HSCT recipients (Supplementary Table S3).[12–29] These studies generally described small patient groups, used varying definitions of CKD, and had a short follow-up period, which is reflected in the large variation in reported CKD incidence after pediatric HSCT.[11–28] In general, severe diseases in childhood, especially malignancies and intensive care unit admissions with AKI, are associated with CKD, which is often progressive in adulthood.[36–39]

The eGFR dynamics in our cohort were largely comparable to studies reporting eGFR dynamics after adult HSCT.[9,10] However, in adults, the eGFR was around 30% lower at all time points. Although the median eGFR was well above the cutoff for CKD at all time points, a 22% reduction of eGFR occurred between pre-HSCT and 10 years after HSCT. Half of this eGFR reduction occurred in the first year after HSCT, during which AKI occurred in 44% of patients. In concordance with the high incidence of AKI early after HSCT, the eGFR at 3 months after HSCT was affected by patients with—or recovering from—AKI. However, at later time points, only steady-state eGFR measurements were included. Remarkably, the other 50% of eGFR reduction occurred between 1 and 10 years after HSCT. Although this reduction is not necessarily clinically significant for an individual patient, the ongoing eGFR reduction in the stable period between 3 and 10 years after HSCT should raise awareness of potential further loss of kidney function in upcoming decades in these young adults and teenagers.

A weakness of this study is the use of SCr-based eGFR formulas. Early after HSCT, poor feeding status, hyperfiltration, and reduced muscle mass might lead to an overestimation of the eGFR calculated with SCr-based formulas. As a result, the increase of muscle mass in the years following HSCT and especially in puberty can reveal CKD that was not recognized at earlier time points.[31,32] In future studies, the addition of cystatin C might improve the evaluation of kidney function after HSCT, although this marker can be affected by inflammation and the use of steroids early after HSCT.[40]

In adult HSCT, repeatedly reported risk factors for CKD are the occurrence of AKI, older age, cyclosporine A use, TBI, and chronic graft-versus-host disease.[4–11,20] Little is known about the risk factors for CKD after pediatric HSCT (Supplementary Table S3). In our study, prolonged severe AKI and hematological malignancy were independent risk factors for CKD. AKI is identified as a risk factor for CKD in most studies in adult HSCT.[4,6–8,20] Although the studies that used the most severe definition of AKI had the highest odds ratio for CKD, no studies investigated the severity of AKI in relation to the development of CKD. The use of KDIGO stages without further specification of eGFR and duration was not discriminative in our cohort of pediatric HSCT recipients. We hypothesize that this is related to hyperfiltration or low muscle mass in a subgroup of patients, allowing a 2-fold or 3-fold increase of creatinine within the normal range of eGFR.

When patients with KDIGO stage ≥2 AKI were further categorized based on lowest eGFR and duration of AKI, a strongly increased risk for CKD was found for patients with prolonged severe AKI. Patients with AKI with eGFR ≥60 ml/min per 1.73 m^2 and even patients with AKI with eGFR <60 ml/min per 1.73 m^2 but recovery within 28 days did not have an increased risk for CKD. As AKI is a frequently occurring complication after pediatric HSCT, this observation helps to identify the children who are at risk for CKD.

In contrast to adult HSCT, hematological malignancy is a major, but no longer the predominant, indication for HSCT in children. Compared with patients with inborn errors of immunity and nonmalignant hematological diseases, patients with hematological malignancy usually receive more potentially nephrotoxic drugs during their treatment before HSCT, which likely explains the increased incidence of CKD.[36,37] The lowest incidence of CKD was observed in patients with inborn errors of immunity. These patients were young (median, 3 years of age) at the time of HSCT and generally received less intensive conditioning before HSCT. Most of these children had not reached pubertal age at the time of evaluation. Therefore, longer follow-up is needed to validate this observation.

In contrast to previous reports in pediatric and adult HSCT,[4,13] we observed a reduced HR of CKD in patients treated with cyclosporine A. However, in the small number of patients who did not receive cyclosporine A, this was due to various clinical reasons. Therefore, no firm conclusions can be drawn from this observation.

Few studies have evaluated proteinuria long-term after HSCT. The incidence of albuminuria in our cohort (14%) was comparable to our earlier study in pediatric HSCT recipients but much higher than the pediatric cohort described by Patzer *et al.*[16,17] In adults, a higher incidence of proteinuria has been described, corresponding with the lower eGFR reported in adults.[6] With 7% of patients having β2-microglobulinuria, tubular damage was not a major problem. We observed hypertension in 9% of long-term HSCT survivors, which is lower than reported in other studies among pediatric or adult HSCT survivors (17%–34%).[9,41,42] In concordance with a study in adult HSCT recipients by Kersting *et al.*,[9] patients with CKD significantly more often had hypertension compared with patients without CKD. Hypertension and diabetes, which are major causes of proteinuria in adults, are frequent early complications of HSCT but often recover within 2 years.[41] Whereas kidney disease is the main cause of hypertension in children, hypertension is most often not of renal origin in adults.[43] In this cohort of teenagers and young adults, correction for hypertension and diabetes mellitus did not affect the results of our multivariate analysis.

Despite therapeutic drug monitoring, avoidance and replacement of nephrotoxic drug combinations, reduction of TBI-based conditioning, and close monitoring of kidney function early after HSCT, we did not observe a reduction of CKD among long-term pediatric HSCT survivors compared with earlier studies.[12–29] We hypothesize that, because of the longer follow-up and strict definitions of CKD, we have recognized more patients with CKD. Recent guidelines for late effects follow-up after pediatric HSCT for both malignant and nonmalignant indications recommend annual evaluation of the renal function in all pediatric HSCT patients.[44–47] Our data support the annual monitoring of eGFR using creatinine and cystatin C, as well as glomerular and tubular proteinuria and blood pressure after pediatric HSCT to identify patients with incipient CKD who could benefit most from nephroprotective interventions, like renin-angiotensin-aldosterone system inhibition and "Dietary Approaches to Stop Hypertension" diet.[48,49] Because CKD may still become evident many years after the initial damage, follow-up of pediatric HSCT survivors into adulthood is essential for a better understanding of long-term renal complications after pediatric HSCT.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Overview of patients with prolonged severe acute kidney injury (AKI).

Table S2. Cox proportional hazards model with correction for diabetes and hypertension.

Table S3. Literature overview of chronic kidney disease after pediatric allogeneic hematopoietic stem cell transplantation.

Figure S1. Covariate-adjusted survival curves for separate nonmalignant HSCT indications.

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