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ORIGINAL ARTICLE

Predictors of kidney complications and analysis of hypertension in children with allogeneic hematopoietic stem cell transplantation

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Abstract

Background This study aimed to determine incidence of kidney complications in pediatric allogeneic hematopoietic stem cell transplantation (HSCT) patients.

Methods Pediatric allogeneic HSCT patients were included. Post-transplantation urinary system complications were collected from medical records and glomerular filtration rates at last visit compared with clinical parameters. Additionally, 24-h ambulatory blood pressure monitoring was performed.

Results The study included 165 pediatric patients. Acute kidney injury (AKI) developed in 125 (75.8%) patients of whom 54 (43.2%) had stage 1, 36 (28.8%) stage 2, and 35 (28%) stage 3 AKI. Primary malignant disease and viral infection post-HSCT were associated with increased risk of AKI (*OR*: 4; 95%*CI*: 1.2–13, $p = 0.022$ and *OR*: 2.9; 95%*CI*: 1.2–6.8, $p = 0.014$, respectively). Mean duration of post-HSCT follow-up was 4.4 ± 2.5 years, during which time 8 patients had chronic kidney disease (CKD) (stage 1, 4 patients; stage 2, 3 patients; stage 3, 1 patient). CKD incidence was higher in patients in whom stem cell product was bone marrow + cord blood and mobilized peripheral blood, compared to bone marrow alone (40–37.5% versus 5.1%, $p = 0.002$). Based on 24-h ABPM, 14.7% and 7.4% of patients with normal office blood pressure had pre-hypertension and hypertension, respectively. In patients with albuminuria/severe albuminuria, daytime and nighttime systolic SDS scores were higher than those without albuminuria/severe albuminuria ($p = 0.010$ and $p = 0.004$, respectively).

Conclusions Incidence of AKI is higher in pediatric HSCT patients with primary malignant disease and those with documented viral infection. Our study highlights the beneficial role of 24-h ABPM as a routine part of standard care of pediatric HSCT recipients.

Keywords Acute kidney injury · Hematopoietic stem cell transplantation · Chronic kidney disease · 24-h ABPM

Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative therapy for pediatric patients with malignant and non-malignant diseases, including bone marrow failure, primary immune deficiencies, inborn errors of metabolism, and autoimmune and autoinflammatory disorders. HSCT involves administration of a conditioning regimen, including high-dose chemotherapy and radiotherapy, prior to stem cell infusion. Hematopoietic stem cells can be sourced from bone marrow, peripheral blood, and cord blood. Additionally, immunosuppressive drugs are used to prevent graft-versus-host disease (GVHD) [1].

Worldwide, approximately 50,000 patients undergo HSCT annually [1]. The number of patients receiving HSCT and their overall survival (OS) have increased

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during the last 2 decades. As the number of HSCT patients and their OS have increased, there has been a significant increase in the number of such patients with transplant-related complications. The HSCT procedure can lead to a variety of early and late complications in several organs/systems. Urinary system complications develop primarily due to the side effects of the conditioning regimen. Among them, acute kidney injury (AKI) has been increasingly recognized as a post-transplant complication related to HSCT, which contributes to acute and chronic morbidity and mortality. The incidence of AKI varies between 20 and 84% in pediatric HSCT patients [2, 3]. The epidemiology of AKI varies greatly because of the lack of a standardized definition of AKI. The underlying etiology of HSCT-related AKI includes conditioning regimen toxicity and/or total body irradiation (TBI), nephrotoxic medications, sepsis, sinusoidal obstruction syndrome (SOS), thrombotic microangiopathy (TMA), and GVHD [1, 2].

Another important kidney complication associated with HSCT is hypertension (HT), which can contribute to the development of chronic kidney disease (CKD). During the first 2 years post-HSCT, > 50% of patients develop HT. Ciclosporin treatment, AKI, TBI, autologous transplantation, obesity, and diabetes are predictors of HT. Effective treatment of HT is crucial for the prevention of CKD and cardiovascular diseases. Data related to the development of HT in HSCT patients, especially pediatric patients, are scarce and based primarily on office measurements [4, 5]. The present study aimed to determine urinary system complications, the predictors of CKD, and the characteristics of HT based on 24-h ABPM in pediatric HSCT patients.

Materials and methods

Patient characteristics

All pediatric patients aged < 18 years who underwent allogeneic HSCT between January 2010 and October 2018 with a follow-up period ≥ 6 months were included in this study. Patients followed up for < 6 months; neonates and patients who did not consent to the study were excluded. Patient clinical and demographic data were obtained from medical records. The study protocol was approved by the Hacettepe University Ethics Committee (GO18/364-07) and written informed consent was obtained from the parents of each patient. The distribution of the patient groups is given in Fig. 1.

Supportive treatment

Throughout the HSCT period, each patient was hospitalized in a single room equipped with a HEPA filter. Patients received acyclovir, fluconazole, and trimethoprim-sulfamethoxazole for prophylaxis against herpes simplex and varicella-zoster viruses, fungal infection, and infection with *Pneumocystis jirovecii*, respectively. Cytomegalovirus (CMV) infection was routinely monitored using real-time PCR assays. Broad-spectrum antibiotic coverage was initiated upon evidence of fever (Tmax > 38 °C). Intravenous immunoglobulin was administered weekly at a standard dose of 400 mg/kg from 1 day prior to HSCT to 21 days post-HSCT, and thereafter depending on the IgG level. Intravenous glutamine, enoxaparin, ursodeoxycholic acid,

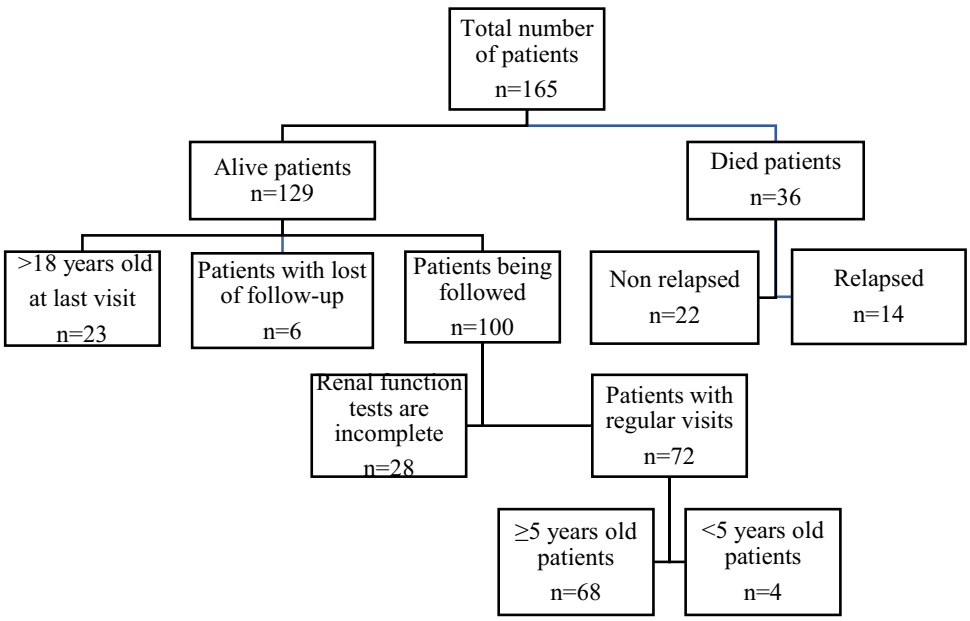

Fig. 1 The distribution of the patients in the study

and vitamin E were given for veno-occlusive disease (VOD) prophylaxis.

Definitions

Neutrophil engraftment was defined as the first of 3 consecutive days with a neutrophil count > 0.5×10^9/L. Platelet engraftment was defined as a platelet count > 20×10^9/L with required transfusion for ≥ 7 days. The absence of hematopoietic recovery on day 60 post-HSCT and autologous hematopoietic reconstruction was considered as engraftment failure. Conditioning regimens were categorized as myeloablative and non-myeloablative based on American Society of Blood and Marrow Transplantation definitions [6]. Acute and chronic GVHD were diagnosed and graded according to Seattle criteria (patients with acute GVHD ≥ stage 2 were classified as acute GVHD) [7, 8]. VOD was diagnosed and staged according to Seattle criteria [9]. Hemorrhagic cystitis (HC) was defined as painful hematuria with a urine culture negative for bacteria and fungus, and without any other explanation, such as general bleeding diathesis or urinary tract catheterization for reasons other than HC, urinary calculi, or bladder neoplasms [10]. Organ toxicity was defined according to National Cancer Institute common toxicity criteria and mucositis was defined according to published standards [11].

Within a 2-week–period prior to initiation of the conditioning regimen, ≥ 2 laboratory measurements were obtained. For the first 3 weeks post-HSCT, the serum creatinine level was checked on a daily basis, and then every other day until discharge. Within 100 days of transplantation, the peak serum creatinine concentration and the day of this measurement were noted. The avoidance of nephrotoxic medications when possible, appropriate fluid administration, stabilization of serum electrolytes, and precautions to prevent further kidney injury were applied for all patients with AKI. Kidney replacement therapy was administered when indicated. AKI was evaluated based on KDIGO classification [12]. All patients with AKI were followed with the department of pediatric nephrology. After discharge, the serum creatinine level was checked biweekly for the first 3 months, and then monthly during the first year post-HSCT. During follow-up, patients with increase in serum creatinine levels or patients with signs of kidney injury (i.e., proteinuria, tubulopathy findings) or with hypertension were referred to the department of pediatric nephrology.

All patients that were regularly followed up were evaluated at the last follow-up visit. Urinalysis and glomerular filtration rate based on creatinine clearance (with 24-h urine collection method) were recorded. Albuminuria is defined as urinary albumin excretion rate (AER) 30–300 mg/day. Severe albuminuria is defined as urinary albumin excretion rate (AER) > 300 mg/day. Office BP measurement was performed for each patient via the auscultation method using an appropriate cuff size on the right arm after ≥ 20 min of rest; the results were evaluated according to the European Society of Hypertension guidelines [13]. Using an AccuWin Pro v3 (SunTech Medical, Inc., Morrisville, NC) device, 24-h ambulatory BP measurement was performed. The device's appropriately sized cuff was placed on the non-dominant arm. All patients were queried about their daily activities and sleep and awake periods. The devices were programmed to measure BP every 20 min during daytime and every 30 min during nighttime. A minimum of 40 valid readings were obtained during the 24-h period and were included in the study for analysis. Patients with regular use of antihypertensive medication continued using these drug(s) during the study. ABPM was standardized using the method of least median of squares, and BP percentiles were evaluated according to Wühl et al.'s [14] reference values according to gender and height. Ambulatory HT was defined as a mean systolic and/or diastolic BP > 95th percentile and systolic and/or diastolic BP load ≥ 25%. Ambulatory pre-HT was defined as a mean systolic and/or diastolic BP < 95th percentile, but systolic and/or diastolic BP load ≥ 25% [15]. A drop in nighttime BP ≥ 10%, as compared to daytime, was defined as dipping, and the absence of such a drop was defined as non-dipping.

Urinary system complications that developed during the first 100 days post-HSCT were defined as early complications and complications that developed after the first 100 days were defined as late complications. Nephrotic syndrome (NS) was defined as proteinuria > 40 mg/m^2/h, hypoalbuminemia, edema, and hyperlipidemia. Thrombotic microangiopathy was defined as direct Coombs negative microangiopathic hemolytic anemia, thrombocytopenia, and AKI. CKD was categorized as 5 stages according to KDIGO classification [16].

Statistical analysis

Descriptive statistical analysis methods were used to evaluate demographic and clinical data. Mean ± SD, median, and IQR (interquartile range) were calculated for numeric variables. Frequency and percentage are used as descriptive values for categorical data. For analysis of the study groups, the chi-square test and Fisher's exact test were used. The *t*-test was used for normally distributed data versus the Mann–Whitney *U* test for non-normally distributed data. Multivariate logistic regression analysis was used

to estimate *OR*s with a 95% *CI*. All data were analyzed using IBM SPSS Statistics for Windows v.21 (IBM Corp., Armonk, NY). The level of statistical significance was set at $p \leq 0.05$.

Results

Patient characteristics

The study included 165 pediatric patients (59 female and 108 male). Mean age of the patients at the time of HSCT was 7.8 ± 5.3 years. All patients had normal glomerular filtration rates at the time of HSCT. Other patient characteristics are given in Table 1.

Table 1 Clinical characteristics of the patients ($n = 165$)

	n (%)
Disease group 1 (malignant)	**39 (23.6)**
Acute lymphoblastic leukemia	20 (12.1)
Acute myeloblastic leukemia	14 (8.5)
Juvenile myelomonocytic leukemia	3 (1.8)
Chronic myeloid leukemia	1 (0.6)
Non-Hodgkin lymphoma	1 (0.6)
Disease group 2 (non-malignant)	**126 (76.4)**
Thalassemia major	33 (20)
Bone marrow failure	30 (18.2)
Congenital immunodeficiency	38 (23)
Neurometabolic disease	13 (7.9)
Hemophagocytic lymphohistiocytosis	12 (7.3)
HLA-matching	
Full-matched	155 (94)
Mis-matched	10 (6)
HSCT source	
Bone marrow	124 (75.1)
Peripheral blood stem cells	32 (19.4)
Bone marrow + umbilical cord	9 (5.5)
Conditioning regimen	
Myeloablative	121 (73.3)
Reduced intensity/non-myeloablative	44 (26.7)
Engraftment failure	6 (3.6)
Acute GVHD	26 (15.8)
Chronic GVHD	23 (13.9)
VOD	36 (21.8)
Viral infection	77 (46.7)
CMV	72 (43.7)
BKV	1 (0.6)
CMV + BKV	4 (2.4)
Death	36 (21.8)
Transplant-related mortality	21 (12.7)
Primary disease–related mortality	15 (9.1)

GVHD graft versus host disease, *HSCT* hematopoietic stem cell transplantation, *VOD* veno-occlusive disease

Post-HSCT kidney complications

According to KDIGO criteria, AKI developed in 125 (75.8%) patients, of whom 54 (43.2%) had stage 1, 36 (28.8%) had stage 2, and 35 (28%) stage 3 AKI. Kidney replacement therapy was performed in 7 patients (peritoneal dialysis: $n = 3$; hemodialysis: $n = 3$; continuous kidney replacement therapy: $n = 1$). Mean time from HSCT to diagnosis of AKI was 34 ± 22 days. Mean age, the male:female ratio, the type of conditioning regimen, the presence of TBI, source of stem cells, HLA compatibility between patient and donor, the presence of VOD, and acute/chronic GVHD did not differ between the patients with and without AKI. In total, 35 (89.7% [35/39]) of the patients with malignant disease (group 1) and 90 of the patients (90/125 [72%]) with non-malignant disease (group 2) had AKI ($p = 0.02$). In addition, 84.4% of the patients (65/77) who experienced viral infection post-HSCT and 68.2% of the patients (60/88), who did not, developed AKI ($p = 0.015$). Multivariate logistic regression analysis showed that primary malignant disease and viral infection post-HSCT were associated with an increased risk of AKI (*OR*: 4; 95% *CI*: 1.2–13, $p = 0.022$ and *OR*: 2.9; 95% *CI*: 1.2–6.8, $p = 0.014$, respectively) (disease group, conditioning regimen, acute GVHD, SOS, viral infection, and AKI were included). During follow-up, only one patient developed TMA; primary disease in this patient was hemophagocytic lymphohistiocytosis. In post-HSCT, none of the patients developed NS.

In all, 28 (17%) patients had HC post-HSCT. Mean age of the patients with HC (15 ± 5.7 years) was higher than that of the patients without HC (10.5 ± 6.1 years, $p = 0.01$). The distribution of gender, type of the conditioning regimen, and the presence of TBI, acute/chronic GVHD, and VOD in patients with and without HC did not differ between the 2 groups. In total, 77 patients had viral infections post-HSCT, of which 17 (22.1%) developed HC. Among the patients who did not have a viral infection, 11 (14.3%) developed HC ($p = 0.077$).

Glomerular filtration rates at the last follow-up visit

In all, 72 patients (31 female and 41 male) could be evaluated at the last follow-up visit. Mean duration of follow-up post-HSCT was 4.4 ± 2.5 years. Mean age of the patients at the last follow-up visit was 10.7 ± 4.0 years. The hematopoietic stem cell source was bone marrow in 59 patients (82%), peripheral blood in 8 patients (11.1%), and bone marrow + cord blood in 5 patients (6.9%). In total, 67 patients were transplanted from full-matched donors and 5 patients were transplanted from mismatched donors. Among these

72 patients, VOD, acute GVHD, and viral infection were observed in 16 (22.2%), 10 (13.9%), and 31 (43%) patients, respectively.

Mean glomerular filtration rate was 139.2 ± 35.7 mL/min/1.73 m^2 and 8 patients had CKD (CKD stage 1: n = 4; CKD stage 2: n = 3; CKD stage 3: n = 1) at the last follow-up visit. Among the 8 patients with CKD, 3 had stage 1 and 1 had stage 3 AKI during the early post-HSCT period. The remaining 64 patients did not have CKD at the last follow-up visit. Among these 64 patients, 20 had stage 1, 14 had stage 2, and 10 had stage 3 AKI (20 patients did not have AKI). Glomerular filtration rates were normal in the remaining patients at the last follow-up visit. The incidence of CKD was higher in the patients in whom HSCT was performed using bone marrow + cord blood and mobilized peripheral blood, as compared to bone marrow (40–37.5% versus 5.1%, p = 0.002) (Table 2).

Laboratory parameters showed that 6 (8.3%) patients had albuminuria. Severe albuminuria was observed as 318 mg/day and 350 mg/day in 2 (2.8%) patients, respectively. Tubular proteinuria was noted in addition to albuminuria in 2 (2.8%) patients and 1 (1.4%) patient had isolated tubular proteinuria. In total, 6 (8.3%) patients had findings consistent with proximal tubulopathy.

Evaluation of blood pressure at the last follow-up visit

Office BP measurement revealed high-normal blood pressure in 3 (4.2%) patients and HT in 1 (1.4%) patient. ABPM was performed in 68 patients aged > 5 years, of whom 12 (17.6%) had pre-HT and 6 (6.6%) had HT (daytime and nighttime systolic and diastolic HT, n = 4; systolic daytime and nighttime HT, n = 1; isolated systolic HT, n = 1). Among the patients, 10 and 5 patients with normal office BP measurement had pre-HT and HT, respectively, based on ABPM measurement (Tables 3 and 4).

Mean systolic and diastolic dipping in the patients was 10.5 ± 5.5% and 15.7 ± 8.3%, respectively. Inverted systolic and diastolic dipping was observed in 2 and 3 patients, respectively.

Table 2 Comparison of the clinical parameters with chronic kidney disease

Parameters		Chronic kidney disease		p value
		No, n (%)	Yes, n (%)	
Diseases	Group 1 (n)	13 (100)	0 (0)	0.185
	Group 2 (n)	51 (86.4)	8 (13.6)	
HSC source	BM (n)	56 (94.9)	3 (5.1)	**0.002**
	BM + Cord blood (n)	3 (60)	2 (40)	
	PBSC (n)	5 (62.5)	3 (37.5)	
HLA matching	HLA full matched (n)	61 (91)	6 (9)	0.092
	HLA mismatched (n)	3 (60)	2 (40)	
Conditioning regimen	Myeloablative (n)	47 (90.4)	5 (9.6)	0.39
	Non-myeloablative (n)	17 (85)	3 (15)	
Total body irradiation	Yes (n)	4 (100)	0 (0)	0.618
	No (n)	60 (88.2)	8 (11.8)	
HSCT number	One (n)	62 (88.6)	8 (11.4)	0.789
	Two (n)	2 (100)	0 (0)	
VOD	Yes (n)	15 (93.75)	1 (6.25)	0.43
	No (n)	49 (87.5)	7 (12.5)	
Hemorrhagic cystitis	Yes (n)	9 (81.2)	2 (18.8)	0.353
	No (n)	55 (90.2)	6 (9.8)	
Acute GVHD	Yes (n)	7 (81.8)	2 (18.2)	0.26
	No (n)	57 (90.5)	6 (9.5)	
AKI	Yes (n)	45 (91.8)	4 (8.2)	0,22
	No (n)	19 (82.6)	4 (17.4)	
Viral infection	Yes (n)	27 (87)	4 (13)	0.478
	No (n)	37 (90.2)	4 (9.8)	
Chronic GVHD	Yes (n)	6 (75)	2 (25)	0,071
	No (n)	58 (90.6)	6 (9.4)	

AKI acute kidney injury, *BM* bone marrow, *GVHD* graft-versus-host disease, *HLA* human leukocyte antigen, *HSC* hematopoietic stem cell, *HSCT* hematopoietic stem cell transplantation, *PBSC* peripheral blood stem cell, *SOS* sinusoidal obstruction syndrome

Table 3 The comparison of office and ambulatory blood pressure measurements

Office BP	ABPM			
	Normotension	Prehypertension	Hypertension	Total, *n* (%)
Normal, *n* (%)	49 (76.6)	10 (15.6)	5 (7.8)	64 (100)
High-normal, *n* (%)	1 (33.3)	1 (33.3)	1 (33.3)	3 (100)
Hypertension, *n* (%)	0	1 (100)	0	1 (100)
Total, *n* (%)	50 (73.5)	12 (17.6)	6 (8.8)	68 (100)

Table 4 The evaluation of ABPM results of the patients

Parameters		ABPM		*p* value
		Normotension	Prehypertension or HTN	
24 h (mean ± SD)	***Systolic*** BP SDS	−0.97 ±1.09	1.22 ± 1.42	0.20
	Diastolic BP SDS	−1.32 ± 1.09	0.82 ± 2.4	**0.02**
	MAP BP SDS	−1.07 ± 1.04	1.22 ± 1.97	**0.02**
Daytime (mean ± SD)	***Systolic*** BP SDS	−1.14 ± 1.05	0.82 ± 1.42	0.20
	Diastolic BP SDS	−1.55 ± 0.89	−0.05 ± 1.82	**0.02**
	MAP BP SDS	−1.24 ± 0.96	0.49 ± 1.67	0.06
Nighttime (mean ± SD)	***Systolic*** BP SDS	−0.61 ± 0.88	1.38 ± 1.28	**0.025**
	Diastolic BP SDS	−0.72 ± 0.92	1.24 ± 1.71	**0.023**
	MAP BP SDS	−0.70 ± 0.93	1.37 ± 1.54	**0.001**
BP load (median, range)	Daytime SBP	2 (0–22)	32 (0–91)	**0.0001**
	Daytime DBP	2 (0–22)	12 (0–86)	**0.0001**
	Nighttime SBP	0 (0–20)	28 (0–86)	**0.0001**
	Nighttime DBP	0 (0–20)	28 (0–100)	**0.0001**
Dipping (mean ± SD)	***Systolic***	11 ± 5.1	8.9 ± 6.2	0.079
	Diastolic	17.3 ± 7.3	11.1 ± 9.2	**0.011**

BP blood pressure, *SDS* standard deviation score

In patients with and without AKI, the median SDS daytime and nighttime systolic values ($p = 0.670$ and $p = 0.495$, respectively) and daytime and nighttime diastolic values ($p = 0.824$ and $p = 0.487$, respectively) did not differ significantly. In total, 15 (22%) patients had extreme isolated diastolic dipping (> 20%) and 4 (5.8%) patients had extreme systolic and diastolic dipping. Mean age, gender, the number of patients in groups 1 and 2, type of conditioning regimen, TBI, HSCT source, matching status, and the presence of HC, VOD, and acute/chronic GVHD did not differ in the patients with pre-HT/HT and normotensive patients. A total of 9 out of 12 patients with pre-HT (75%) and 5 out of 6 patients with HT (83.3%) had AKI in the acute period. The incidence of AKI was not different in patients with pre-HT/HT and normotensive patients ($p = 0.284$). Moreover, 2 out of 12 patients with pre-HT (16.7%) and 2 out of 6 patients with HT (33.3%) had CKD at last visit. The incidence of CKD was not different in patients with pre-HT/HT and normotensive patients ($p = 0.111$).

Among the patients with pre-HT based on ABPM, only 2 were using steroids. In addition, 2 of the patients with HT were using steroids and 3 patients were using calcineurin inhibitors. In all, 2 patients were using antihypertensive medications, of which 1 patient with TMA was being treated with Ca channel blockers (0.2 mg/kg/day) and an angiotensin-converting enzyme inhibitor (ACEi) (enalapril at a dose of 0.3 mg/kg/day); her office BP was consistent with pre-HT and ABPM showed uncontrolled systolic and diastolic BP. The other patient had normal ABPM, but was treated with ACEi (enalapril at a dose of 0.3 mg/kg/day) due to congenital heart disease (atrial septal defect).

In the patients with albuminuria/severe albuminuria, daytime and nighttime systolic SDS scores were higher than in the patients without albuminuria/severe albuminuria ($p = 0.010$ and $p = 0.004$, respectively). Daytime and nighttime diastolic SDS scores did not differ significantly between the patients with and without albuminuria/severe albuminuria ($p = 0.065$ and $p = 0.090$, respectively). SDS scores for the daytime and nighttime MAP values were higher in the patients with albuminuria/severe albuminuria than in those without albuminuria/severe albuminuria ($p = 0.023$ and $p = 0.028$, respectively).

Discussion

The present study investigates the incidence and risk factors of kidney complications, development of CKD over time, and the characteristics of HT at the last follow-up visit in

pediatric HSCT patients. The present findings show that viral infection and primary malignant disease are important risk factors for AKI post-HSCT. The incidence of CKD is higher in cases of some stem cell sources, in patients with mismatched donors, and in patients with chronic GVHD. Among the present study's patients, 10 and 5 patients with normal office BP had pre-HT and HT, respectively, based on ABPM measurement.

There are many risk factors for the development of AKI. The risk factors for AKI post-HSCT include recipient-related factors (age, history of AKI, and low pre-HSCT GFR), HSCT related factors (allogeneic HSCT, unrelated donor, TBI, HLA mismatched transplantation, myeloablative conditioning, and nephrotoxic drugs), and post-HSCT complications (sepsis, hyperbilirubinemia, VOD, GVHD, and TMA). The reported incidence of AKI post-HSCT varies greatly due to differences in AKI diagnostic criteria [2].

The literature includes some studies on post-HSCT AKI in pediatric patients. The reported incidence of AKI in HSCT recipients varies between 21 and 84%. This wide range of incidence is most likely because of variances in populations, patient characteristics, and nonstandard definitions of AKI. There are many possible factors for our relatively high rate of incidence of AKI. First, the incidence of AKI is higher with allogeneic HSCT patients compared to autologous HSCT patients. Another factor may be the type of conditioning regimen. Myeloablative (conventional) allogeneic HSCT involves the use of high-dose chemotherapy to treat the underlying disease. In some studies, AKI is not different in patients undergoing a myeloablative vs. reduced intensity conditioning regimen [17]. However, in some other studies, a myeloablative regimen had more risk for acute toxicity like AKI [1]. In our cohort, 73.3% of the patients had myeloablative regimen. Hazar et al. [18] prospectively studied 34 pediatric patients with a median age of 8.2 years, of whom 53% had hemoglobinopathy as the primary disease. The researchers defined post-HSCT AKI as 100% increase in the pre-HSCT serum creatinine level, or a higher than the normal level for age and gender during the first 3 months post transplantation. They found that 26.4% of the patients had AKI within 100 days of transplantation, but none of the patients required kidney replacement therapy. In addition, ciclosporin was observed to be a risk factor for AKI.

İleri et al. [19] prospectively studied AKI incidence in 57 pediatric HSCT patients based on AKIN criteria. Similar to the present study, they divided the patients into malignant ($n = 17$) and non-malignant ($n = 40$) disease groups. They reported an AKI incidence rate of 42%. Ciclosporin A, amphotericin B, and sinusoidal obstruction syndrome were observed to be risk factors for post-HSCT AKI. More recently, Kurokawa et al. [20] studied the kidney outcome in 69 pediatric patients during the first 100 days post-HSCT based on AKIN criteria. In all, 60.9% of the patients had malignant disease. The cumulative incidences of stage 1, stage 2, and stage 3 AKI were 14.6%, 15.3%, and 50.7%, respectively. The researchers noted that malignant disease and hyperferritinemia (> 1000 ng/mL) were the most significant independent risk factors for stage 3 AKI. Koh et al. [3], based on AKIN criteria, reported an AKI incidence rate of 68.7%, which is similar to that noted in the present study. In study of Raina et al., HSCT conducted for malignant and non-malignant indications did not have any impact on AKI incidence [17]. In the present study, the incidence of AKI was 75.8%, and 72% of the patients had stage 1 or 2 AKI. Moreover, logistic regression analysis showed that primary malignant disease and viral infection post-HSCT are important risk factors of AKI. Patients with primary malignant disease use higher doses of nephrotoxic chemotherapy drugs before HSCT than patients without malignant disease. Additionally, patients with malignant disease are more likely to have infections necessitating use of nephrotoxic antibiotics than patients without malignant disease. We think that all of these factors can cause deterioration of glomerular filtration rate during the acute period after HSCT. In the present study, another important risk factor for AKI was viral infection. In total, 84.4% of the patients with viral infections had AKI; the nephrotoxic effects of antiviral drugs might have contributed to the development of AKI.

Raina et al. published a consensus report regarding AKI in HSCT patients. They reported patients with VOD had higher risk of AKI and should be closely monitored for the development of AKI [17]. However, in our study, patients with VOD (SOS: sinosoidal obstruction syndrome) did not have any increased risk for AKI in multivariant analysis. They also reported recommendations/suggestions for the follow-up and management of TMA which is another well-known complication of HSCT. In our cohort, only one patient had TMA. Raina et al. recommended/suggested that serum BUN and creatinine should be screened at a minimum 6 months and 1-year posttransplant [17]. However, in our cohort, serum creatinine level was checked biweekly for the first 3 months, and then monthly during the first year post-HSCT, which may be another reason for the high AKI incidence.

Numerous studies have shown that HT is an important and potentially modifiable risk factor for severe cardiovascular outcomes [21]. HT is also common in both adult and pediatric HSCT recipients, as compared to the general population. Among pediatric and adult HSCT patients, ≤ 70% have HT during the first 2 years post procedure. The predictors of HT include treatment with ciclosporin, AKI, TBI, receipt of an autologous transplant, obesity, and diabetes [1]. Data regarding HT in HSCT recipients are primarily based on adult data and/or office BP measurements. In the present study, office BP showed high-normal BP and HT in 4 patients; however, ABPM showed that in 15 patients

with normal office BP, 10 had pre-HT and 5 had HT. The benefits of 24-h BP monitoring during the early post-HSCT period are significant [1]; however, the present findings show that 24-h ABPM should also be used in the standard care of pediatric HSCT patients during the later post-HSCT periods. In an earlier study, we investigated post-transplant HT in 29 pediatric kidney transplant recipients and observed that 13 (45%) patients had newly diagnosed untreated HT and all of the patients were either on daily or alternate doses of prednisolone [22]. In the present study, only 7.3% of the patients had HT according to the ABPM findings. In contrast to solid organ transplant recipients, HSCT patients can discontinue immunosuppression in the absence of active GVHD, which might explain the low incidence of HT in the present cohort.

Pao et al. [4] conducted an important study on the ABPM profile of HSCT patients. They included 60 patients aged > 12 years who survived through day 80 post transplantation. The median patient age was 48 years (range: 14–69 years); however, 4 and 17 patients, respectively, were aged 14–17 years and 18–39 years. In their cohort, 72% of the patients had HT based on ABPM, which is higher than that in the present study. In total, 15% of their patients had diabetes or use insulin, and 6.7% were not receiving immunosuppression therapy. The age characteristics, comorbid diseases, and high rate of immunosuppression might explain the higher rate of HT in the present study. In addition, in their study, micro/macroalbuminuria was present in 31.7% of the patients, which is also higher than in the present study (11.1%). In the present study, patients with albuminuria/severe albuminuria had higher daytime and nighttime systolic and MAP SDS than the patients without albuminuria/severe albuminuria.

CKD is another important complication of HSCT and long-term follow-up data on glomerular filtration rate are limited. The cumulative incidence of CKD varies between 7 and 48%, and it can occur 6 months–10 years after transplantation. Progression to kidney disease occurs in approximately 4% of HSCT patients [1]. In earlier studies, the incidence of CKD was higher than in more recent studies. A retrospective study by Kist-van Holthe et al. [23] showed that CKD occurred in 28% of children 1 year post-HSCT. In a prospective study of theirs, the incidence of CKD in children who underwent HSCT between 1998 and 2000 was 10% [24]. They also noted that the sole predictor of CKD was a high pre-HSCT serum creatinine level. A prospective study performed by Frisk et al. [25] with a median follow-up period of 10 years showed that in the TBI group, mean GFR decreased from 124 to 99 mL/min/1.73 m^2 6 months post-HSCT, but that there was not a difference between patients with and without TBI. Another prospective study by İleri et al. [19] that included 57 pediatric HSCT patients reported that 1 year post-HSCT, 10% of patients had CKD and that none of them required dialysis. In addition, no parameter was noted to be a predictor of CKD. In the present study, mean post-HSCT follow-up was > 4 years and CKD was observed in 11% of the patients. Moreover, the incidence of CKD was higher in the patients in whom HSCT was performed using bone marrow + cord blood and peripheral blood than in those who received bone marrow alone. Although not statistically significant, patients with mismatched donors and patients with chronic GVHD had higher incidence of AKI. These 3 factors might have led to the intensive use of immunosuppressive drugs, resulting in the development of CKD. Recently, Lugthart et al. investigated longitudinal follow-up of estimated glomerular filtration rates in 216 pediatric HSCT recipients. They found that 17% of the patients developed CKD within 10 years after HSCT which is higher than the present study. Hematological malignancy as HSCT indication was an independent risk factor for CKD [26].

Although the present study analyzed in detail the kidney complications of HSCT, there are some limitations. Firstly, dosage and trough levels of the nephrotoxic drugs used could not be analyzed. Secondly, the collection of data on other potential variables that might affect the development of AKI could not be performed.

In conclusion, the present findings show that the incidence of AKI is higher in pediatric HSCT patients with a primary malignant disease and in those with documented viral infection, indicating the importance of close follow-up and monitorization for kidney assessment. On the other hand, the findings show that the incidence of CKD is higher in patients in whom the stem cell source was either bone marrow + cord blood or mobilized peripheral blood than in those who receive bone marrow. Lastly, the present findings highlight the beneficial role of 24-h ABPM as a routine part of the standard care of pediatric HSCT patients.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Anar Gurbanov, Bora Gulhan, and Barış Kuşkonmaz. The first draft of the manuscript was written by Anar Gurbanov and Bora Gulhan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Hingorani S (2016) Renal complications of hematopoietic-cell transplantation. N Engl J Med 374:2256–2267
2. Raina R, Herrera N, Krishnappa V, Sethi SK, Deep A, Kao WM, Bunchman T, Abu-Arja R (2017) Hematopoietic stem cell

transplantation and acute kidney injury in children: a comprehensive review. Pediatr Transplant 21(4). https://doi.org/10.1111/petr.12935
3. Koh KN, Sunkara A, Kang G, Sooter A, Mulrooney DA, Triplett B, Onder AM, Bissler J, Cunningham LC (2018) Acute kidney injury in pediatric patients receiving allogeneic hematopoietic cell transplantation: ıncidence, risk factors, and outcomes. Biol Blood Marrow Transplant 24:758–764
4. Pao E, Gove NE, Flynn JT, Hingorani S (2018) Ambulatory blood pressure and endothelial dysfunction in hematopoietic cell transplantation recipients. Biol Blood Marrow Transplant 24:1678–1684
5. Hoffmeister PA, Hingorani SR, Storer BE, Baker KS, Sanders JE (2010) Hypertension in long-term survivors of pediatric hematopoietic cell transplantation. Biol Blood Marrow Transplant 16:515–524
6. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, Apperley J, Slavin S, Pasquini M, Sandmaier BM, Barrett J, Blaise D, Lowski R, Horowitz M (2009) Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 15:1628–1633
7. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED (1974) Clinical manifestations of graft versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 18:295–304
8. Storb R, Prentice RL, Sullivan KM, Shulman HM, Deeg HJ, Doney KC, Buckner CD, Clift RA, Witherspoon RP, Appelbaum FA, Sanders JE, Stewart PS, Thomas ED (1983) Predictive factors in chronic graft versus-host disease in patients with aplastic anemia treated by bone marrow transplantation from HLA-identical siblings. Ann Intern Med 98:461–466
9. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED (1984) Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology 4:116–122
10. Tsuboi K, Kishi K, Ohmachi K, Yasuda Y, Shimizu T, Inoue H, Matsumoto M, Hattori K, Yoshiba F, Watanabe S, Ogawa Y, Kawada H, Yabe H, Yabe M, Kato S, Hotta T (2003) Multivariate analysis of risk factors for hemorrhagic cystitis after hematopoietic stem cell transplantation. Bone Marrow Transplant 32:903–907
11. Zanis-Neto J, Flowers ME, Medeiros CR, Bitencourt MA, Bonfim CM, Setúbal DC, Funke V, Sanders J, Deeg HJ, Kiem HP, Martin P, Leisenring W, Storb R, Pasquini R (2005) Low-dose cyclophosphamide conditioning for haematopoietic cell transplantation from HLA-matched related donors in patients with Fanconi anemia. Br J Haematol 130:99–106
12. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1–138
13. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, Invitti C, Litwin M, Mancia G, Pall D, Rascher W, Redon J, Schaefer F, Seeman T, Sinha M, Stabouli S, Webb NJ, Wühl E, Zanchetti A (2016) 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34:1887–1920
14. Wühl E, Witte K, Soergel M, Mehls O, Schaefer F, German Working Group on Pediatric Hypertension (2002) German working group of pediatric hypertension. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. J Hypertens 20:1995–2007
15. Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, Zachariah JP, Urbina EM, American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young (2014) Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension 63:1116–1135
16. KDIGO AKI Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:1–138
17. Raina R, Abu-Arja R, Sethi S, Dua R, Chakraborty R, Dibb JT, Basu RK, Bissler J, Felix MB, Brophy P, Bunchman T, Alhasan K, Haffner D, Kim YH, Licht C, McCulloch M, Menon S, Onder AM, Khooblall P, Khooblall A, Polishchuk V, Rangarajan H, Sultana A, Kashtan C (2022) Acute kidney injury in pediatric hematopoietic cell transplantation: critical appraisal and consensus. Ped Nephrol. https://doi.org/10.1007/s00467-022-05448-x
18. Hazar V, Gungor O, Guven AG, Aydin F, Akbas H, Gungor F, Tezcan G, Akman S, Yesilipek A (2009) Renal function after hematopoietic stem cell transplantation in children. Pediatr Blood Cancer 53:197–202
19. Ileri T, Ertem M, Ozcakar ZB, Ince EU, Biyikli Z, Uysal Z, Ekim M, Yalcinkaya F (2010) Prospective evaluation of acute and chronic renal function in children following matched related donor hematopoietic stem cell transplantation. Pediatr Transplant 14:138–144
20. Kurokawa M, Nishiyama K, Koga Y, Eguchi K, Imai T, Oba U, Shiraishi A, Nagata H, Kaku N, Ishimura M, Honjo S, Ohga S (2020) Hyperferritinemia and acute kidney injury in pediatric patients receiving allogeneic hematopoietic cell transplantation. Pediatr Nephrol 35:1977–1984
21. Armenian SH, Chemaitilly W, Chen M, Chow EJ, Duncan CN, Jones LW, Pulsipher MA, Remaley AT, Rovo A, Salooja N, Battiwalla M (2017) National Institutes of Health hematopoietic cell transplantation late effects initiative: the cardiovascular disease and associated risk factors working group report. Biol Blood Marrow Transplant 23:201–210
22. Gülhan B, Topaloğlu R, Karabulut E, Ozaltın F, Aki FT, Bilginer Y, Beşbaş N (2014) Post-transplant hypertension in pediatric kidney transplant recipients. Pediatr Nephrol 29:1075–1080
23. Kist-van Holthe JE, van Zwet JM, Brand R, van Weel MH, Vossen JM, van der Heijden AJ (1998) Bone marrow transplantation in children: consequences for renal function shortly after and 1 year post-BMT. Bone Marrow Transplant 22:559–564
24. Kist-van Holthe JE, Bresters D, Ahmed-Ousenkova YM, Goedvolk CA, Abbink FC, Wolterbeek R, Bredius RG, Pauwels EK, van der Heijden AJ (2005) Long-term renal function after hemopoietic stem cell transplantation in children. Bone Marrow Transplant 36:605–610
25. Frisk P, Bratteby LE, Carlson K, Lönnerholm G (2002) Renal function after autologous bone marrow transplantation in children: a long-term prospective study. Bone Marrow Transplant 29:129–136
26. Lugthart G, Jordans CCE, de Pagter APJ, Bresters D, Jol-van der Zijde CM, Bense JE, van Rooij-Kouwenhoven RWG, Sukhai RN, Louwerens M, Dorresteijn EM, Lankester AC (2021) Chronic kidney disease ten years after pediatric allogeneic hematopoietic stem cell transplantation. Kidney Int 100:906–914