

The incidence of acute kidney injury in children undergoing allogeneic hematopoietic stem cell transplantation: A pilot study

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Abstract

Background. Acute kidney injury (AKI) is a common feature in adults undergoing allogeneic hematopoietic stem cell transplantation (alloHSCT). However, accurate assessment of AKI incidence in the pediatric population still seems a challenge.

Objectives. To evaluate the incidence of AKI according to the pRIFLE criteria in children undergoing alloHSCT, with special focus on differences between patients transplanted due to oncological and non-oncological indications.

Material and methods. A retrospective analysis of data, concerning 135 children undergoing alloHSCT due to oncological (89 patients) or other (46 patients) reasons, was performed. The values of estimated glomerular filtration rate (eGFR) were measured before alloHSCT, 24 h after, 1, 2, 3, 4, 8 weeks, 3 and 6 months after alloHSCT, and the AKI incidence was analyzed.

Results. Acute kidney injury was diagnosed in 54% of all patients. The Risk stage (R) was noticed at least once in 46% of oncological and 37% of non-oncological children. The Injury stage (I) concerned 12% of oncological and 6% of non-oncological patients undergoing alloHSCT. The incidence of AKI in both groups was comparable. The mean eGFR values in oncological children were higher than those in the non-oncological patients even before transplantation and until the 4th week after alloHSCT. The eGFR increased significantly in all patients 24 h after alloHSCT and returned to pre-transplantation records after 2–3 weeks. Then, oncological patients demonstrated a gradual decrement of eGFR. Six months after transplantation, eGFR values in oncological children were significantly lower compared to pre-transplantation records, whereas in non-oncological children, these values were comparable.

Conclusions. Although the type of indication for alloHSCT has no impact on the AKI incidence, children undergoing alloHSCT due to oncological reasons are at greater risk of renal impairment 6 months after transplantation than non-oncological patients.

Key words: acute kidney injury, estimated glomerular filtration rate, hyperfiltration, pRIFLE criteria

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Introduction

Hematopoietic stem cell transplantation (HSCT) is a recognized treatment method in children, and the indications for it are being constantly expanded.^{1–4} The pediatric population undergoing HSCT is unique in that a substantial number of patients require transplantation as a therapeutic tool against inborn anomalies. Thus, apart from dominating oncological reasons, there is a growing number of non-oncological indications for HSCT in children, such as aplastic anemia, immunodeficiencies or metabolic diseases.^{1,3} Aggressive therapy is associated with the occurrence of numerous side effects and the development of life-threatening complications.^{5–8} In the early post-transplantation period, management of opportunistic infections and symptoms associated with graft-versus-host disease (GVHD) constitute the main issue. Moreover, the majority of the transplantation-related conditions, including GVHD, hypertension, sepsis, or drug nephrotoxicity, compose the list of risk factors for acute kidney injury (AKI).⁹

In the light of these findings, AKI in pediatric patients undergoing HSCT seems to be an underestimated problem. Multicenter analyses, concerning all children hospitalized due to AKI, have shown that HSCT patients constitute the most numerous group among them.¹⁰ World reports also show alarming data on up to 34% of HSCT patients in whom AKI turns into chronic kidney disease.^{11,12}

So far, there have been few publications attempting to assess the scale of kidney damage in children undergoing hematopoietic stem cell allotransplantation (alloHSCT).^{13,14} A systematic review, performed in Australia, has reported the incidence of AKI in children after HSCT as between 11% and 42%, based on changes in absolute serum creatinine values or decrease in diuresis.¹⁵ American data indicate a significantly higher incidence of AKI (up to 84%), based on the pediatric (p)RIFLE criteria defining subsequent stages of acute kidney injury (Risk, Injury, Failure, Loss of function, End stage kidney disease).¹⁶ The latter seem to be a more suitable way of AKI evaluation in children, because they take into account the eGFR variability instead of serum creatinine absolute values, which strongly depend on muscle mass and hydration status.¹⁷

However, none of these reports took into account the pediatric specificity of patients qualified for HSCT, nor compared the subpopulations of patients transplanted due to oncological and non-oncological reasons.

Objectives

Therefore, the objective of the study was to assess the AKI incidence based on the pRIFLE criteria in children undergoing alloHSCT in the early, intermediate and late post-transplantation period, with distinction between children transplanted because of oncological and non-oncological reasons.

Material and methods

A retrospective analysis concerned medical records of 178 patients undergoing first (173 children) or next (5 patients) alloHSCT in the Department of Bone Marrow Transplantation, Pediatric Oncology and Hematology (Wrocław Medical University, Poland) in the years 2016–2018. The observation period started before introducing conditioning therapy, then control examinations were performed in the early (after 24 h, and then after 1, 2, 3 and 4 weeks), intermediate (after 8 weeks and 3 months) and late (after 6 months) post-transplantation period.

The exclusion criteria for the patients were the age below 2 years and over 18 years. The patients' age varied from 1.5 months to 26 years. One hundred thirty-five out of 178 children (78 boys and 57 girls) met the age criteria (mean age: 8.27 ± 5.14 years). They were divided into 2 groups according to the indications for allotransplantation: oncological or other.

The 1st group consisted 89 patients (53 boys, 36 girls; mean age: 9.84 ± 4.34 years) qualified for transplantation due to oncological reasons. The detailed indications are given in Fig. 1. Forty-five percent of these patients were classified as a high-risk group according to specific treatment protocols, while 22% experienced recurrence. A total of 17% of children underwent alloHSCT as a standard intervention, consistent with the primary disease protocol; the rest underwent transplantation due to the failure of previous therapy. In 71% of cases, the donor was unrelated, in 23% – related and in 6% – haploidentical.

The 2nd group included 46 patients (25 boys, 21 girls; mean age: 9.16 ± 4.78 years) who underwent alloHSCT following non-oncological indications, listed in detail in Fig. 2. A total of 72% of children underwent alloHSCT from an unrelated donor, 24% from a related donor and 4% from a haploidentical donor.

The serum creatinine concentrations were assessed in the fixed time points according to the hematological

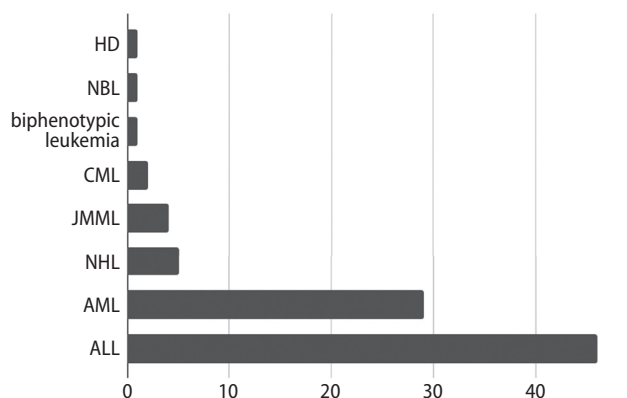


Fig. 1. Quantity of patients with oncological indications for alloHSCT

HD – Hodgkin disease; NBL – neuroblastoma; CML – chronic myeloid leukemia; JMML – juvenile myelomonocytic leukemia; NHL – non-Hodgkin disease; AML – acute myeloblastic leukemia; ALL – acute lymphoblastic leukemia.

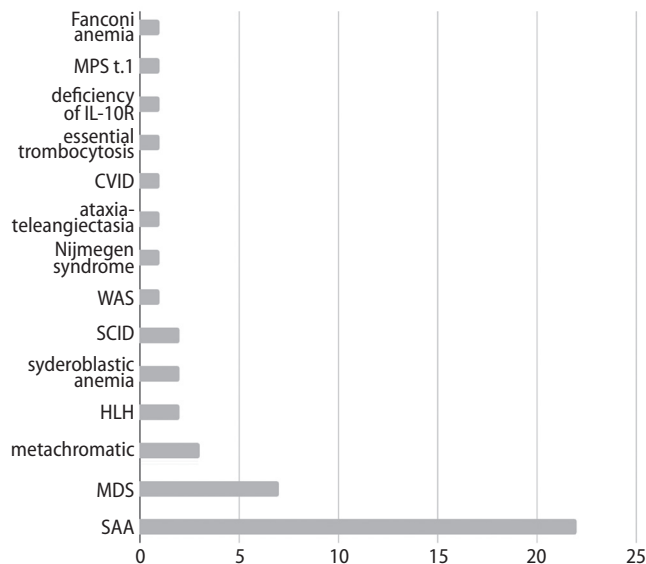


Fig. 2. Quantity of patients with non-oncological indications for alloHSCt

MPS t. 1 – mucopolysaccharidosis type 1; CVID – common variable immunodeficiency; WAS – Wiskott–Aldrich syndrome; SCID – severe variable immunodeficiency; HLH – hemophagocytic lymphohistiocytosis; MDS – myelodysplastic syndrome; SAA – severe aplastic anemia.

protocols: before conditioning, 24 h after allotransplantation, and then 1 week, 2, 3, 4, 8 weeks, and 3 and 6 months after alloHSCt. The creatinine concentration was measured using modified Jaffé method and eGFR was calculated based on the Schwarz formula.¹⁸ The eGFR changes were confronted with the pre-transplantation values.

In the majority of patients, conditioning therapy was myeloablative (busulfan, cyclophosphamide and fludarabine or fludarabine, treosulfan, thiotepa); the minority followed the non-myeloablative (cyclophosphamide, fludarabine) regimen. The protocol of prophylaxis against GVHD contained pre-HSCT ATG, cyclosporine A from 1 day before HSCT and methotrexate given in the 1st, 3rd and 6th day after transplantation. Ninety-eight out of 135 (69% of oncological and 77% of non-oncological) patients developed GVHD.

Acute kidney injury was diagnosed based on the pRI-FLE criteria.¹⁷ Hyperfiltration was defined according to recent pediatric guidelines and meta-analysis as eGFR ≥ 140 mL/min/1.73 m².^{19,20}

Continuous variables were reported as mean \pm standard deviation (SD), and categorical variables as frequencies and percentages. The comparisons of continuous variables were performed with analysis of variance (ANOVA) and Student's t-test. The relations between categorical variables were tested with χ^2 test or Fisher's exact test. A value of $p < 0.05$ was considered significant. All calculations were carried out with the use of STATISTICA v. 13.3 (StatSoft Inc., Tulsa, USA).

All procedures were performed in accordance with the 1964 Declaration of Helsinki and its further amendments. The retrospective waiver of consent was obtained from the University Hospital ethical committee.

Results

Patients undergoing alloHSCt due to oncological reasons were more numerous than those transplanted because of non-oncological conditions. The mean eGFR values were above 90 mL/min/1.73 m² in all patients before transplantation, independent of the underlying disease (Fig. 3,4). None of the patients presented with eGFR < 60 mL/min/1.73 m² before alloHSCt. The peak eGFR values were observed 1 day and 1 week after alloHSCt in both groups (Fig. 3,4). Then, they returned to those observed before the treatment after 1 week (non-oncological patients) or after 2 weeks (oncological patients). From that turning point, mean eGFR in oncological children remained lower than before alloHSCt and decreased significantly at each time point from the 4th week until the 6th month of observation

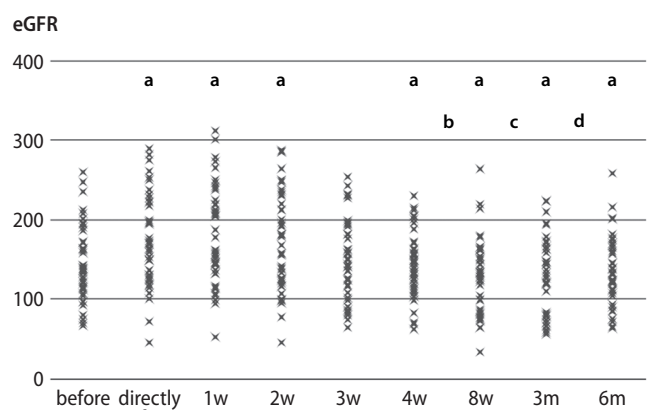


Fig. 3. The values of estimated glomerular filtration rate (eGFR) in oncological patients

before – before alloHSCt; directly after – 24 h after alloHSCt; 1w – 1 week after alloHSCt; 3m – 3 months after alloHSCt; a – $p < 0.05$ any time point compared to before alloHSCt; b – $p < 0.05$ 8 weeks compared to 4 weeks after alloHSCt; c – $p < 0.05$ 3 months compared to 8 weeks after alloHSCt; d – $p < 0.05$ 6 months compared to 3 months after alloHSCt.

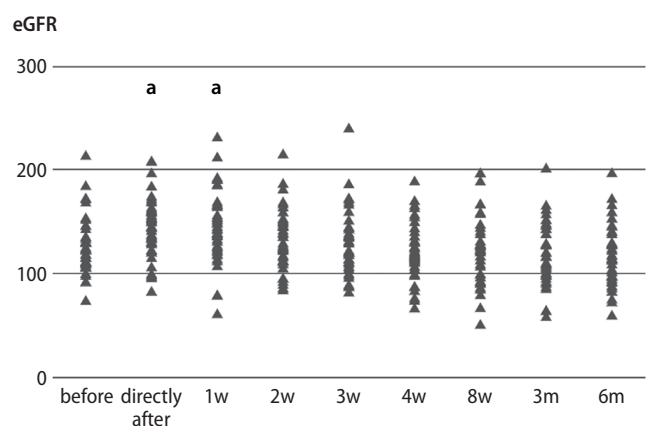


Fig. 4. The values of estimated glomerular filtration rate (eGFR) in non-oncological patients

before – before alloHSCt; directly after – 24 h after alloHSCt; 1w – 1 week after alloHSCt; 3m – 3 months after alloHSCt; a – $p < 0.05$ any time point compared to before alloHSCt.

Table 1. Incidence of acute kidney injury in examined patients

Pediatric(p)RIFLE criteria		1 day after alloHSCt	1 week after alloHSCt	2 weeks after alloHSCt	3 weeks after alloHSCt	4 weeks after alloHSCt	8 weeks after alloHSCt	3 months after alloHSCt	6 months after alloHSCt
Oncological patients	Risk (↓ eGFR > 25%)	1 (1.1%)	0	7 (7.9%)	13 (14.6%)	16 (18.0%)	31 (34.8%)	21 (23.6%)	18 (20.2%)
	Injury (↓ eGFR > 50%)	1 (1.1%)	0	1 (1.1%)	1 (1.1%)	0	2 (2.2%)	6 (6.7%)	0
Non-oncological patients	Risk (↓ eGFR > 25%)	0	1 (2.2%)	4 (8.9%)	3 (6.7%)	9 (20.0%)	8 (17.8%)	8 (17.8%)	5 (11.1%)
	Injury (↓ eGFR > 50%)	1 (2.2%)	0	0	0	0	1 (2.2%)	1 (2.2%)	0

eGFR – estimated glomerular filtration rate; alloHSCt – allogeneic hematopoietic stem cell transplantation.

(Fig. 3). Contrarily, mean eGFR in non-oncological patients remained stable and comparable to pre-transplantation records, from the 3rd week until the 6th month of follow-up (Fig. 4).

The incidence of AKI at subsequent time points before and after alloHSCt varied with time (Table 1). In the entire time interval (0–6 months after transplantation), 54% of patients demonstrated the features of AKI according to the pRIFLE criteria. The risk stage (R) appeared at least once in 58 patients (41 oncological and 17 non-oncological) and the injury stage (I) in 14 patients (11 oncological and 3 non-oncological). The biggest number of AKI episodes was noticed 8 weeks after alloHSCt and the R incidence was then significantly higher in oncological than in non-oncological patients ($\chi^2 = 4.5$; $p = 0.034$). None of the patients experienced the failure stage (F) with eGFR decrease exceeding 75%.

After 6 months, oncological patients demonstrated significantly diminished eGFR values compared to the pre-transplantation records, whereas in non-oncological children these values were comparable (Fig. 3,4). In 12 children, eGFR values varied between 60 mL/min/1.73 m² and 89 mL/min/1.73 m², whereas in 2 patients eGFR dropped below 60 mL/min/1.73 m².

During the observation period, 10 patients died (0.7%). One death was a direct consequence of allotransplantation (20 days after HSCT), while the remaining ones were associated with late, non-nephrological complications. None of the patients, observed for up to 6 months, required renal replacement therapy.

Discussion

The incidence of AKI throughout the 6-month observation period in our study group was as high as 54%. Our data are concordant with the estimations performed by other authors, stressing the importance of renal function follow-up in the post-HSCT period.^{13,15,16}

Indeed, the post-HSCT renal dysfunction is a well-documented phenomenon among adult patients, analyzed from

the perspectives of AKI incidence, other comorbidities, long-term outcome, and mortality.²¹ Recent meta-analysis proved that, despite progress in diagnosing AKI, its incidence in adults remains high and affects more than 50% of patients undergoing HSCT.²² However, analyses in pediatric patients concentrated rather on the impact of AKI on overall mortality or long-term prognosis than on aspects of early renal dysfunction and its consequences.^{13–16}

The higher incidence of AKI among patients after allo-transplantation compared to autotransplantation is also well-known and has justified our decision to concentrate on children undergoing alloHSCt.^{22,23} The pediatric specificity gave us a unique opportunity to confront the 2 subpopulations – those with the flagship oncological reason for HSCT with those who had indications like immune deficiencies and inborn metabolic disorders, non-existent in adult patients qualified for HSCT. We have reported the preponderance of children transplanted due to oncological reasons over those treated with HSCT because of non-oncological indications. The evaluation of AKI incidence in the whole group revealed that R was diagnosed over 4 times more often than I. In detail, R concerned 43% of all children after alloHSCt (46% of oncological and 37% of non-oncological patients), whereas I affected 10% of the whole studied group (12% of oncological patients and less than 1% of non-oncological patients). Despite discrepancies in the number and percentage of patients affected by R or I between 2 subgroups, these differences reached statistical significance at only 1 time point. Eight weeks after transplantation, the R incidence was higher among oncological patients compared to non-oncological children.

The pattern of fluctuations in the AKI incidence also seemed similar in both groups. The number of R patients peaked between the 4th and 8th week after alloHSCt (irrespective of the analyzed group), then stabilized (non-oncological) or even diminished (oncological) until the 6th month of observation. Patients classified to I were clinically significant in number only in the oncological population 3 months after alloHSCt. Otherwise, single cases were noticed throughout the whole observation period.

The similar overall AKI incidence and its fluctuations during observation period in both groups may result from the fact that there were no significant differences in treatment regimens or severity of complications between oncological and non-oncological patients. The vast majority of children followed myeloablative protocols and similar GVHD prophylaxis. The incidence of GVHD or infections did not differ between the subgroups.

However, the abovementioned similarity in both subgroups stayed in contrast with the parameters of renal function. The eGFR values and the incidence of hyperfiltration were significantly higher in oncological compared to non-oncological patients. Hyperfiltration is a recognized condition in children with malignancies, increasing in frequency with subsequent cycles of chemotherapy and connected with the patients' hypermetabolic state.²⁴ The routine procedures during first 3 weeks after HSCT, like intravenous nourishment and additional fluid intake at the amount of 3 L/m²/day with subsequent administration of diuretics if needed, may add to already increased eGFR values. Indeed, in our patients a significant elevation of eGFR values was detected 24 h and one week after alloHSCT.


Therefore, the eGFR discrepancy between oncological and non-oncological patients, persisting only until the 4th week after the procedure, was aggravated by iatrogenic interventions. When intravenous supplementation was ceased, the tendency reversed and from the 8th week after alloHSCT eGFR values were similar in both groups. However, an alarming trend appeared from the 4th week after alloHSCT. The eGFR values in oncological patients decreased systematically until the 6th month of observation. Such a result may suggest possible long-term renal function deterioration, but longer observation is needed to confirm this hypothesis.

Our study has limitations. This retrospective report contained data collected according to hematological protocols. Therefore, a few nephrological aspects are missing, such as urine output or cystatin C measurements. Both groups were heterogeneous, especially in the case of non-oncological patients. The majority of patients were followed up regularly only until the 3rd month after alloHSCT; some of them were then transferred to the hematological centers near home. Thus, the analysis longer than 6 months was not possible.

Conclusions

The AKI incidence in children undergoing alloHSCT is independent of indication for this procedure, whereas eGFR values seem conditioned by previous chemotherapy in oncological patients. Children undergoing alloHSCT due to oncological reasons are at a greater risk of renal dysfunction 6 months after transplantation than the population with non-oncological indications for this therapy.

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