Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 6

Acute Kidney Injury in Patients with Leukaemia Submitted to Allogeneic Hematopoietic Stem Cell Transplant – KDIGO Classification with Creatinine and Urinary Output Criteria: Cohort Analysis

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Received: 25 Dec 2022
Accepted: 02 Feb 2023
Published: 10 Feb 2023
J Short Name: COO

Citation:

Rodrigues N. Acute Kidney Injury in Patients with Leukaemia Submitted to Allogeneic Hematopoietic Stem Cell Transplant – KDIGO Classification with Creatinine and Urinary Output Criteria: Cohort Analysis. Clin Onco. 2023; 6(18): 1-10

Keywords:

Acute kidney injury; Hematopoietic stem cell transplant; Leukaemia; Epidemiology

1. Abstract

1.1. Background: Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT) is often complicated by Acute Kidney Injury (AKI) and has been increasingly used in patients with leukaemia. Studies on this subject include patients with several haematological diseases and use only Serum Creatinine (SCr) to define AKI. We aimed to evaluate incidence, risk factors and 5-year prognostic impact of AKI in patients with leukaemia submitted to allo-HSCT by SCr and Urinary Output (UO).

1.2. Methods: We conducted a single-centre retrospective cohort study. AKI was defined according to KDIGO classification. We used survival analysis methods considering competing events - the Fine and Gray method - to identify AKI risk factors and assess the impact of AKI on disease-free survival. Additive Cox proportional hazards regression models were applied to analyse time until death from all causes. Stepwise selection regression methods were used to create the final multivariable model.

1.3. Results: We included 164 patients. The cumulative incidence of AKI was 63.4% 100 days post-HSCT. On the first day of AKI, 76.9% presented SCr criteria, 15.4% presented UO criteria and 7.7% presented both criteria. The highest stage of AKI was 1 in 61.8%, 2 in 21.6% and 3 in 16.7%. Variables independently associated with AKI: HCT-CI >2 (HR:1.88,95%CI:1.13-3.11;p=0.015), radiotherapy in the past (HR:2.07,95%CI:2.07-1.06;p=0.034), LDH at hospital admission (HR:1.51,95%CI:1.03-2.21;p=0.035), shock (HR:1.57,95%CI:1.02-2.39;p=0.039), and sepsis (HR:3.36,95%CI:1.22-9.24;p=0.019). Severe AKI was independently associated with lower overall survival along the first 5 years (HR:1.76,95%CI:1.03-3.00;p=0.037).

1.4. Conclusion: AKI in leukaemia patients submitted to allo-HSCT had a cumulative incidence of 63.4% and more than 15% of these patients presented only with UO reduction on the day of AKI onset. Two thirds of the patients evolved with AKI stage 2 or 3. Sepsis, previous radiotherapy treatments at any time before HSCT, HCT-CI scoring higher than 2 points, shock and higher LDH levels increased the risk of developing AKI. Severe AKI was associated to lower overall survival throughout the first five years after allo-HSCT. To our knowledge, this is the first study considering both SCr and UO for AKI patients with Leukaemia submitted to allogeneic Hematopoietic Stem Cell Transplant.

2. Introduction

The incidence of most haematological malignancies has been increasing and leukaemia are no exception [1]. Allogeneic Hematopoietic Stem Cell Transplant (allo-HSCT) has shown to provide significantly better survival rates in patients with different types of leukaemia [2] and it is now often used worldwide. Therefore, it is important to understand the complications of allo-HSCT in these patients and analyse them separately from patients submitted to HSCT for other causes.

A known complication of HSCT is Acute Kidney Injury (AKI). AKI is mostly found in the first 100 days after HSCT and has been associated with poor outcomes [3-5]. Given the knowledge that AKI after HSCT could increase mortality [6], several studies have been published. The AKI incidence in different modalities of HSCT ranged from 20% to 92% [7]. In myeloablative allo-HSCT AKI incidence varied between 27 and 66% and in non-myeloablative it is thought to complicate up to half of the transplanted patients [4,5,8,9].

The wide range of AKI incidence reported in these studies is explained by different baseline haematologic diagnoses and by the heterogeneity of AKI definitions.

The most recent definition of AKI, Kidney Disease Improving Global Outcomes (KDIGO) classification [10], was proposed in 2012 and resulted from the fusion of the former classifications Risk Injury Failure Loss of kidney function End-stage kidney disease - RIFLE in 2004, and Acute Kidney Injury Network AKIN in 2007 [11,12] (RIFLE and AKIN).The AKI definition by KDIGO classification includes an increase in serum creatinine (SCr) of at least ≥0.3 mg/dL or ≥50% within 48 hours or Urinary Output (UO) of <0.5 mL/kg/hour for at least 6 hours. The definition also considers three severity stages.

Recent studies focusing on AKI by KDIGO classification in allo-HSCT have not considered UO criteria. Some authors have used weekly values rather than daily values of creatinine [13-16] for study populations with a variety of haemato-oncologic diagnosis.

SCr variability as only criteria for AKI may be insufficient. Creatinine production is proportional to muscle mass (often diminished in patients with leukaemia), and its level in the blood can be elevated in catabolic states as well as reduced in fluid overload. Patients submitted to allo-HSCT experience hemodynamic variabilities that can lead to creatinine reduction and subsequent underestimation of AKI. A rapid reduction of UO may be the earliest indicator of decreased kidney function in AKI patients in general and it can be the only change detectable in an AKI episode.

Studies on AKI in allo-HSCT include patients with leukaemia, lymphoma, and multiple myeloma. The treatment approach and specific characteristics of each subgroup – such as age incidence, comorbidities, exposure to different chemotherapy regimens prior to allo-HSTC, history of autologous HSCT, indication for allo-HSCT as well as prognosis of the haematological disease itself may influence the results when determining risk factors of AKI.

Our study aims to 1) determine incidence and severity of AKI in leukaemia patients submitted to allo-HSCT using KDIGO classification with both SCr and UO criteria in the first 100 days of HSCT, 2) to identify independent risk factors for AKI in these patients and 3) to evaluate the association of AKI during this period with disease-free survival and overall survival at 5 years of allo-HSCT.

3. Materials and Methods

We conducted a single-centre retrospective cohort study. We included patients with leukaemia admitted at Centro Hospitalar Universitário Lisboa Norte, EPE (CHULN) between January 2005 and December 2015 for allo-HSCT. We included allo-HSCT with myeloablative and Reduced Intensity (RIC) conditioning treatments, with unrelated, related, matched, and mismatched donors and both bone marrow and peripheral blood source of stem cell progenitors. We excluded patients under the age of 18 years; patients with chronic kidney disease already on renal replacement therapy; patients who underwent renal replacement therapy one week before transplantation and patients with previous autologous or allogeneic HSCT.

The specific conditioning schemes used followed institutional protocols based on the subtype of leukaemia and patient´s characteristics. Total body irradiation is not available at CHULN, EPE, and it is not contemplated in any of the institutional protocols. All patients received cyclosporine for Graft-Versus-Host Disease (GVHD) prophylaxis associated with methotrexate in myeloablative allo-HSCT or mofetil mycophenolate in RIC allo-HSCT. Prophylactic antimicrobial therapy included ciprofloxacin, co-trimoxazole, fluconazole and acyclovir.

Our data collection was based on daily medical records, six-hour period nurses´ records and diagnostic exams during hospital admission period for allo-HSCT, as well as all routine medical records and laboratorial analysis before and after allo-HSCT.

We collected variables related to patient demographic characteristics (age, gender, race, body weight and height); related to patient comorbidities (diabetes mellitus, hypertension, arrhythmia, valvular heart disease, ischemic heart disease, cerebrovascular disease, hepatic chronic disease, intestinal inflammatory disease, peptic ulcer, connective tissue disease, chronic obstructive pulmonary disease, solid cancer, psychiatric disease); related to leukaemia (subtype, number of previous chemotherapy cycles, exposure to radiotherapy in the past); related to allo-HSCT (type of donor, cells source, induction regimen, period of aplasia, length of stay in hospital, blood results on hospital admission day for HSCT, sinusoidal obstructive syndrome, sepsis, nephrotoxic drugs, hypovolemia, shock, Intensive Care Unit, AKI, AKI stage, graft-versus-host disease, cytomegalovirus infection). For the proposed outcomes, time of disease relapse and time of all-cause mortality were also collected.

All patients were followed until they died or censored - patients were censored at 60 months (5 years) after allo-HSCT - this timeline was defined because after this 5-year period patients are often transferred to other hospitals near their residence.

3.1. Definitions

Serum creatinine baseline was considered to be the serum creatinine level registered at hospital admission before conditioning regimen - generally two weeks before cells´ infusion day.

Glomerular filtration rate at baseline was estimated according to CKD-EPI equation [17], using serum creatinine baseline defined above.

AKI was defined by KDIGO clinical practice criteria [10] (any of the following: Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or UO <0.5 ml/kg/h for 6 hours) and Stage of AKI followed KDIGO classification considering the worst serum creatinine value and/or longest period of UO reduction during hospital stay for HCT – Stage 1 corresponded to an increase in serum creatinine of >0.3 mg/dL or 1.5–1.9 times baseline or UO < 0.5 ml/kg/h for 6–12 hours; Stage 2: serum creatinine increase by 2.0–2.9 times baseline or UO < 0.5 ml/kg/h for 12 hours; Stage 3 (AKI-3): serum creatinine increase by 3.0 times baseline or the serum creatinine increase to >4.0 mg/dL or UO < 0.3 ml/kg/h for 24 hours or anuria for 12 hours. Severe AKI was defined as AKI stage 3.

Daily values of serum creatinine and 6-hour urinary output were considered for AKI diagnosis since the first day of allo-HSCT until hospital discharge as well as other hospital in-stays and weekly evaluation in outpatient clinic until 100 days after allo-HSCT.

The Hematopoietic Cell Transplantation – specific Comorbidity Index (HCT-CI) [18] was calculated according to the latest validated version. Radiotherapy in the past included any radiotherapy treatments performed on any part of the body from haematological diagnosis day until HSCT, taking into consideration that total body radiation was never performed.

Nephrotoxic drugs included gentamicin, amikacin, vancomycin, amphotericin B, foscarnet.

Relapse free survival was calculated in months from HSCT until disease relapse - defined by the presence of ⩾5% of blasts, which were found in the Bone Marrow (BM) by morphological analysis. Overall survival was calculated in months from allo-HSCT until any cause of death.

3.2. Ethical Committee

This study was approved by the local Ethical Committee in agreement with institutional guidelines. Due to the retrospective and non-interventional nature of the study, informed consent was waived by the Ethical Committee.

3.3. Statistical Methods

Categorical variables were described as frequencies (percentages) and quantitative data as median (P25 = 25th percentile; P75 = 75th percentile). The main outcomes were AKI cumulative incidence, disease-free survival, and overall survival. For the two first outcomes, statistical methodology suggested by the European Group for Blood and Marrow Transplantation [19] was used, namely survival analysis methods considering competing events by the Fine and Gray method [20]. Accordingly, death was considered as the competing risk in the univariable and multivariable analyses to identify AKI risk factors and assess the impact of AKI on disease-free survival. Additive Cox proportional hazards regression models were applied to analyse time until death from all causes. Stepwise selection regression methods were used to create the final multivariable model. The Cox proportional hazards assumption was checked using formal statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. Because this assumption was violated for the binary variable corresponding to the relapse (yes vs. no), a model with time-varying coefficients was fitted to the data [21]. Crude and adjusted hazard ratios were estimated with corresponding 95% Confidence Intervals (CIs). A level of significance α=0.05 was considered. Data analysis was performed with the statistical software package STATA for Windows (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) and R software (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

4. Results

Between January 2005 and December 2015, 209 patients diagnosed with leukaemia were submitted to allo-HSCT in our centre. Among these patients, 45 patients had at least one exclusion criteria and 164 patients were eligible for the study. Demographic and clinical patients' characteristics are shown in table 1.

4.1. Incidence, presentation criteria and severity of AKI

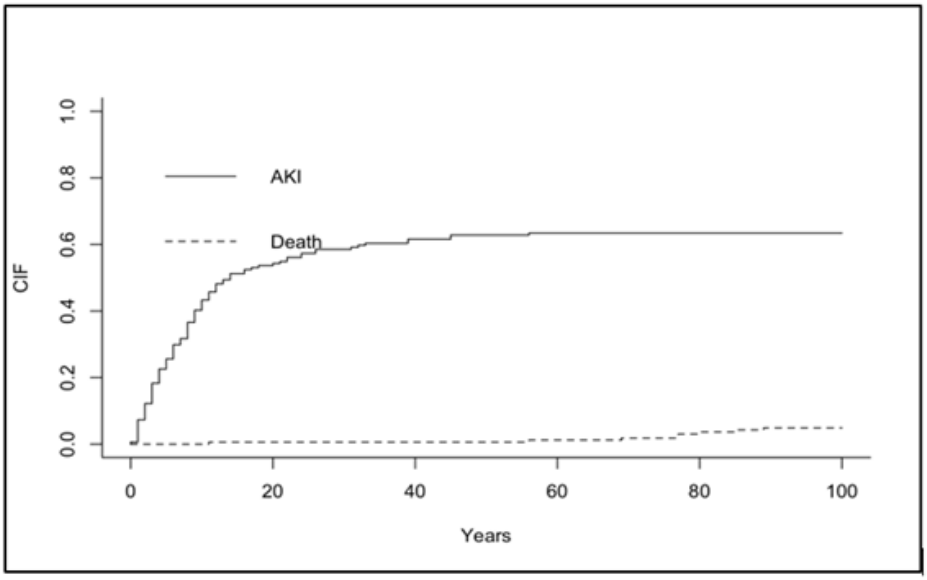
AKI Cumulative Incidence (CI) considering death as a competing event was 58.5% at day 30 and 63.4% at day 100 after HSCT (Figure 1).

Considering only AKI patients: on the first day of AKI onset, 76.9% presented SCr criteria, 15.4% presented UO criteria and 7.7% presented both criteria. According to the severity of AKI on the first day of AKI onset, 80.8% of patients presented with stage 1, 16.4% presented with stage 2, and 2.9% of patients presented with stage 3. As AKI developed, the highest severity stage reached was stage 1 in 61.8% of AKI patients, stage 2 in 21.6% of AKI patients, and stage 3 in 16.7% of AKI patients.

Table 1: Patients' baseline characteristics and transplant related variables.

Patients Characteristics and transplant related variables	Category	n (%)	P50	P25	P75
Age at transplant (years)			39.1	28.1	50.4
Gender	Female	89(54.3)			
	Male	75 (45.7)			
Race	Caucasian	150 (91.5)			
	non Caucasian	14 (8.5)			
BMI (Kg/m2)			23.2	20.9	25.3
HCT-CI	0-1	140 (85.5)			
	≥2	24(14.5)			
Hematologic Diagnosis	AML	91 (55.5)			
	ALL	55 (33.5)			
	CML	14 (8.5)			
	Others	4 (2.4)			
Nr of previous cycles of therapy			3	2	4
Radiotherapy in the past		11 (6.7)			
baseline eGFR			115	100	130
Chronic Kidney Disease	eGFR < 60	9 (5.5)			
	stage 3a	7 (4.3)			
	stage 3b	2 (1.2)			
Induction Regimen	Non-myeloablative (RIC)	117(71.3)			
	Myeloablative	47(28.7)			
Donor	Related donor	92(56.1)			
	Unrelated/panel donor	72(43.9)			
Progenitor cells source	peripheral blood	142(86.6)			
	bone marrow	22(13.4)			
Period of aplasia (days)			11	10	13
Sepsis		147(89.6)			
Nephrotoxic drugs		136(82.9)			
Hypovolemia		64(39.0)			
Shock		41 (25.0)			
ICU stay		13 (7.9)			
GVHD *		117(71.3)			
CMV		53(32.3)			
TMA/ TLS/ VOOS		6(0.04)			
At hospital admission day:					
Haemoglobin (gr/dl)			11.3	9.4	12.9
Leukocytes (cells/mm3)			4330	2700	6340
Neutrophils (cells/mm3)			2110	1160	3520
Lymphocytes (cells/mm3)			1030	610	1600
Platelets (/μl)			150000	69000	200000
Urea (mg/dl)			31	25	40
Uric Acid (mg/dl)			4.9	3.7	5.6
Calcium (mg/dl)			9.3	8.8	9.7
Phosphate (mg/dl)			3.8	3.2	4.3
Reactive C Protein (mg/dl)			1	0.3	2.3
Lactate Dehydrogenase (U/L)			352	283	467
Alanine Transaminase (U/L)			31	19	47
Total Bilirubin (mg/dl)			0.5	0.4	0.7

Legend table 1: BMI - body mass index; RIC (reduced-intensity regimen); HCT CI - hematopoietic stem cell transplant comorbidity index; Nr – number; ICU - intensive care unit; GVHD* - Graft versus Host Disease during hospital stay for HSCT; CMV – cytomegalovirus; TMA/ TLS/ VOOS – Thrombotic microangiopathy/Tumor Lysis Syndrome/ Sinusoidal obstruction syndrome.



Time	0	10	20	40	60	80	100
AKI cumulative incidence	0.006098	0.4329	0.542683	0.615854	0.6346	0.63455	0.63455
Death cumulative incidence	0	0	0.006098	0.006098	0.0124	0.03797	0.05081
N. Risk for AKI	164	98	76	63	61	60	60

Figure 1: AKI cumulative incidence function and incidence estimates at time points

4.2. Analysis of the association between patients' baseline characteristics and transplant related variables with AKI incidence

The univariable analysis considering death as a competing risk is presented in Table 2. In this analysis variables associated with AKI incidence were: HCT-CI>2 (HR:1.79;95%CI:1.14-2.80;p=0.011), radiotherapy in the past (HR:2.22;95%CI:1.21-4.05;p=0.009), leucocytes count at hospital admission (HR:1.02;95%CI:1.01-1.03;p<0.001 considering each increase of 1000 leucocytes/L), lymphocytes count at hospital admission (HR:1.02;95%CI:1.02-1.03;p<0.001 considering each increase of 1000 lymphocytes/L), serum lactate dehydrogenase at hospital admission (HR:1.60;95%CI:1.27-2.02;p<0.001 considering each increase of 1000 units/L), sepsis (HR:3.82;95%CI:1.30-11.2;p=0.015), mechanical ventilation (HR:1.96;95%CI:1.30-2.95;p=0.001), ICU stay (HR:2.30;95%CI:1.38-3.83;p<0.001).

Variables independently associated with a higher incidence of AKI are shown in Table 3 and included: HCT-CI>2 and radiotherapy in the past with almost a double risk of AKI (HR: 1.88; 95% CI:1.13-3.11) and (HR: 2.07; 95% CI:2.07-1.06), respectively, shock (HR: 1.57; 95% CI:1.57-2.39), LDH with a 51% increase in the risk of AKI for each increment of 1000 units/L (HR: 1.51; 95% CI:1.03-2.21), and sepsis with an approximately three-fold higher risk (HR: 3.36; 95% CI:1.22-9.24).

We summarized in a flow chart the study design and the AKI Incidence, presentation criteria, severity, and risk factors .

4.3. AKI prognostic impact in patients' overall survival

Considering the first 5 years following allo-HSCT, 106 (64,6%) patients died. The median overall survival was 12.11 months (P25=3.96; P75=59.13)

Analysing overall survival, the univariable analysis showed that the variables with an impact on lower overall survival during this period were AKI (HR:1.85;95%CI:1.21-2.82;p=0.004), severe AKI (HR:3.26;95%CI:1.95-5.44;p <0.001), sepsis (HR:3.19;95%CI:1.57-2.39;p=0.039), shock (HR:4.63;95%CI:3.06-7.00;p<0.001), relapse (HR:1.62;95%CI:1.09-2.40;p=0.016), leucocytes count (HR considered for each rise of 1000 leucocytes:1.03:95%CI:1.01-1.05 ;p=0.001), and serum lactate dehydrogenase (HR for each 1000 units/L increment:4.35, 95%CI:2.15-8.80;p<0.001). Multivariable analysis identified variables with an independent impact on overall survival and results are shown in Table 4.

Accordingly, patients with severe AKI had almost a double risk (HR:1.76, 95% CI:1.03-3.00) (Figure 2), shock was associated with approximately a four-fold risk of AKI (HR:4.48, 95%CI:2.84-7.06), relapse presented a higher risk after 13 months of HSCT than before this time (HR in the first 13 months of HSCT:2.00, 95%CI:1.33-3.02 and HR after 13 months of HSCT:14.39, 95%CI:5.92-34.99), leucocytes count (for each 1000 leucocytes increment there is an increase of 2%: HR:1.02, 95%CI:1.01-1.05) and serum lactate dehydrogenase was associated with a 32% increase in the risk for each 1000 units/L increment (HR:1.32;95% CI:2.15-8.80).

Considering the disease-free survival, variables with an impact on time until relapse were radiotherapy in the past with almost a three-fold higher risk of relapsing (HR: 2.92, 95%CI:1.25-6.83; p=0.013) and serum Alanine transferase with a 1% increase in the risk of relapse for each unit increment of this enzyme (HR:1.01, 95%CI:1.00-1.01;p=0.011).

Table 2: Competing risks regression. Univariable analysis for AKI

Patients Characteristics	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Age at transplant (years)	0.98	0.68	1.44	0.94
Gender (reference category female)	1.18	0.81	1.72	0.38
Race	0.64	0.35	1.18	0.15
BMI (Kg/m2)	1.03	0.98	1.07	0.23
HCT-CI ≥2	1.58	1.14	2.8	0.011
Hematologic Diagnosis:				
AML comparing ALL	0.7			0.099
AML comparing CML	0.96			0.923
AML comparing Others	2.4			0.098
ALL comparing CML	0.73			0.36
CML comparing Others	0.4			0.127
Nr of previous cycles of therapy	1.06	0.97	1.14	0.21
Radiotherapy in the past	2.22	1.21	4.05	0.009
baseline eGFR	0.99	0.98	1.01	0.46
Induction Regimen (reference category myeloablative)	1.27	0.84	1.95	0.26
Donor (reference category related donor)	0.99	0.67	1.46	0.94
Progenitor cells source (reference category bone marrow)	1.47	0.68	0.86	0.16
GVHD prophylaxis (reference category methotrexate)	1.27	0.84	1.95	0.26
Period of aplasia (days)	1.01	0.99	0.96	0.61
Sepsis	3.82	1.3	11.2	0.015
Nephrotoxic drugs	1.5	0.97	2.32	0.067
Hypovolemia	1.44	0.99	2.08	0.055
Shock	2.07	1.41	3.02	<0.001
Mechanical Ventilation	1.96	1.3	2.95	0.001
ICU stay	2.3	1.38	3.83	<0.001
GVHD *	1.04	0.7	1.54	0.85
CMV infection	1.37	0.94	2	0.1
TMA/ TLS/ VOOS	1.73	0.75	4	0.2
At hospital admission day:				
Haemoglobin (gr/dl)	1.03	0.94	1.12	0.56
Leukocytes (cells/mm3)*	1.02	1.01	1.03	<0.001
Neutrophils (cells/mm3)*	1.01	0.99	0.95	0.74
Lymphocytes (cells/mm3)*	1.02	1.02	1.03	<0.001
Platelets (/µl)*	1.01	0.99	0.98	0.47
Urea (mg/dl)	0.99	0.97	1.01	0.54
Uric Acid (mg/dl)	1.1	0.97	1.25	0.13
Calcium (mg/dl)	1.08	0.79	1.48	0.63
Phosphate (mg/dl)	1.01	0.8	1.28	0.91
Reactive C Protein (mg/dl)	1	0.95	1.06	0.92
Lactate Dehydrogenase (U/L)	1.6	1.27	2.02	<0.001
Albumin (gr/dl)	1.12	0.86	1.46	0.4
Alanine Transaminase (U/L)	0.99	0.99	1	0.13
Total Bilirubin (mg/dl)	0.85	0.51	1.39	0.52

Legend table 2: BMI - body mass index; RIC (reduced-intensity regimen); HCT CI - hematopoietic stem cell transplant comorbidity index; HSCT - hematopoietic stem cell transplant; AML – Acute Myeloid Leukaemia; ALL – Acute Lymphoblastic Leukaemia; CML - Chronic Myeloid Leukaemia; ICU - intensive care unit; GVHD* - Graft versus Host Disease during hospital stay for HSCT; CMV – cytomegalovirus; TMA/ TLS/ VOOS – Thrombotic microangiopathy/Tumour Lysis Syndrome/ Sinusoidal obstruction syndrome.

Table 3: Competing risks multivariable regression analysis for AKI

Patients and transplant related Characteristics	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
HCT≥2	1.88	1.13	3.11	0.015
Radiotherapy in the past	2.07	1.06	4.03	0.034
Shock	1.57	1.02	2.39	0.039
Sepsis	3.36	1.22	9.24	0.019
LDH at admission*	1.51	1.03	2.21	0.035

c-index = 0.635; 95% CI = (0.576; 0.694)

Legend table 3: HCT CI - hematopoietic stem cell transplant comorbidity index; LDH – Lactate dehydrogenase; *considering each 1000 units/L increment

Table 4: Multivariable Cox regression for mortality.

Patients and transplant related Characteristics	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Leucocytes at admission	1.02	1.01	1.05	0.009
LDH at admission	3.73	2	6.95	<0.001
Severe AKI in the first 100 days	1.76	1.03	3	0.037
Shock	4.48	2.84	7.06	<0.001
Relapse in the first 13 months of HSCT	2	1.33	3.02	0.001
Relapse after 13 months of HSCT	14.39	5.92	34.99	<0.001

Legend Table 4: LDH – lactate dehydrogenase; AKI – Acute Kidney Injury; HSCT – Hematopoietic Stem Cell Transplant

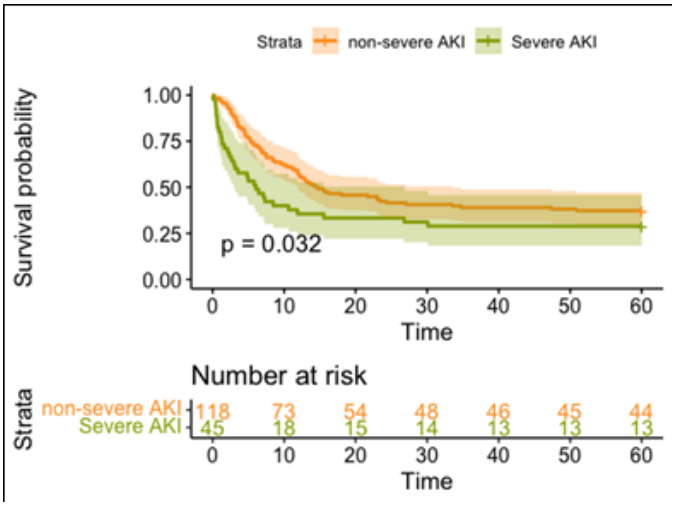


Figure 2: Overall survival in months according to severe AKI.

5. Discussion

The scientific community is becoming aware of the importance of AKI in allo-HSCT given the expansion of this procedure and the knowledge of this complication in general. In fact, several revision articles [5,6,22,23] and even tutorials [24] on this matter have been published recently on this matter by international societies.

Considering AKI incidence in allo-HSCT using different AKI classifications, data by Lopes et al showed a 27% creatinine-doubling [9] , Bao et al presented a 49% incidence using RIFFLE classification, Parikh et al presented a 59% incidence of creatinine-doubling [4], Mori et al presented 62% incidence in AKI by AKIN [25]. In 2020, Kanduri et al published a meta-analysis including studies between 1995 and 2019 with an estimated incidence of AKI in HSCT of 55.1% [26].

Recent studies applying SCr criteria for KDIGO classification in allo-HSCT were published by Gutierrez-Garcia et al [13], presenting a 63,4% AKI incidence when considering weekly SCr measures, by Sakagushi et al [27], presenting a 64.9% AKI incidence and Andronesi et al [28], showing 68.9% AKI incidence. These studies included not only patients with leukaemia – who are often submitted to allo-HSCT as first line therapy after chemotherapy has provided disease remission - but also patients with other hemato-oncological diseases - such multiple myeloma (affecting older patients with more previous comorbidities) and lymphoma where indication for allo-HSCT comes after long periods of chemotherapy with higher burden of immunosuppression with nephrotoxic drugs and in most cases previous autologous HSCT that have failed treating the underlying disease.

We found a cumulative incidence of 63.4% of AKI. Our study included only patients with leukaemia and AKI definition by KDIGO was made using both SCr and UO criteria. We would expect to have higher incidence ok AKI by using more diagnostic criteria for AKI than other studies but AKI incidence was slightly lower in our study when compared to AKI incidence in studies that used only SCr criteria in populations with more comorbidities, higher exposure of chemotherapy and even previous auto HSCT. This suggests that these differences may contribute for AKI in allo-HSCT in other populations and prospective studies considering specific groups of hematologic diseases are needed.

In our study, on the first day of AKI onset three quarters of the patients presented initially with stage 1 but more than two thirds evolved with AKI stage 2 or 3. Also, more than 15% of AKI patients were firstly diagnosed by UO criteria. This finding reinforces the importance of UO in early diagnosis and, consequently, early approach to AKI.

Although some studies failed to find an independent association between sepsis and AKI in HSCT, we were expecting this result considering the multiple interaction pathways between these two entities and its known association in other AKI scenarios. This finding was also shown by Liu et al [29]. Also, Andronesi et al [28] reported the association between sepsis and AKI stage 3.

The independent association between an HCT-CI score higher than 2 points and AKI incidence enhanced the impact of even low comorbidity burden in AKI. In our study, patients had lower HCT-CI scores than most studies concerning AKI in HSCT adult populations – explained by our focus in patients with leukaemia and thus generally younger and previously healthy.

We were expecting to find an association with estimated glomerular filtration rate at baseline and AKI given that chronic kidney disease is a known risk factor for AKI in general. But in our study only 6 patients had glomerular filtration rates lower than 60 ml/min/1,73m2 – and only one lower that 45 ml/min/1,73m2, so chronic kidney disease had very low incidence.

Previous studies have shown an association between total body irradiation and AKI in allogeneic HSCT. Total body irradiation was not performed in any of our patients, but patients submitted to previous radiotherapy treatment of any corporal region at any time before HSCT showed higher AKI incidence. This finding corroborates experimental studies suggesting that exposure to radiation results in subclinical renal fibrosis that persists through time making patients prone to AKI [30].

LDH was pointed by Geva et al [31], as a key prognostic factor in acute myeloid leukaemia and lymphoma patients undergoing allogeneic HSCT by showing an association between lactate dehydrogenase levels the day before conditioning regimen and death. Our results reinforce the importance of taking this marker in consideration as a surrogate for pre-transplant risk-stratification as we also found an independent association with AKI.

In our study, patients submitted to myeloablative conditioning regimen did not have statistically significant higher AKI incidence compared to patients submitted to non-myeloablative conditioning regimen. Although Parikh et al and other studies reached significance comparing non myeloablative regimen to myeloablative regimen [8], our results are shared by Mori et al 2012 on their work with allogeneic HCT patients [25] and are also referred by JA Lopes et al 2016 [6].

Considering our results, AKI was not significantly associated with lower overall survival considering the first 5 years after allo-HSCT, but patients with severe AKI had almost twice the risk (HR:1.76, 95% CI:1.03-3.00). Although some studies have not found an association between AKI and lower overall survival [13], in allo-HSCT in general, the systematic review and meta-analysis of Kanduri et al [26], on the subject concluded that Pooled odds ratios of 3-month mortality and 3-year mortality among patients undergoing HSCT with AKI were 3.05 (95% CI 2.07–4.49) and 2.23 (95% CI 1.06–4.73), respectively, with higher mortality in more severe stages.

In the present study some limitations have to be acknowledged. The single-center and retrospective nature of the study with a small cohort of patients may compromise, at least in part, the results of our study. Despite these limitations, our study has noteworthy strengths – we focused exclusively in patients with leukaemia in order to reduce bias related to the different haematological diagnoses and we used not only creatinine criteria but also UO criteria to diagnose and categorize AKI - to the best of our knowledge, this is the first study considering both SCr and UO for AKI by KDIGO classification in patients with leukaemia submitted to allo-HSCT.

More studies are needed in this population of patients defining AKI by KDIGO classification through both creatinine and urinary output criteria, particularly prospective studies.

6. Conclusion

In our study, AKI in leukaemia patients submitted to allo-HSCT had a cumulative incidence of 63.4%. More than 15% of AKI patients were firstly diagnosed by UO criteria. Although three quarters of the patients presented with AKI stage 1 on the first day of AKI onset, more than two thirds evolved with AKI stage 2 or 3.

Sepsis, previous radiotherapy treatments at any time before HSCT, HCT-CI scoring higher than 2 points, shock and higher LDH levels increased the risk of developing AKI. Severe AKI was associated to lower overall survival throughout the first five years after allo-HSCT.

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