

Original article

Acute kidney injury after allogeneic hematopoietic stem cell transplantation – Predictors and survival impact: A single center retrospective study

Maria do Mar Menezes^{a,*}, Ana Isabel Marques^b, Teresa Chuva^a, Carlos Pinho Vaz^b, Hugo Ferreira^a, Rosa Branca^b, Ana Paiva^a, António Campos^b, José Maximino Costa^a

^a Serviço Nefrologia, Instituto Português de Oncologia do Porto, Porto, Portugal

^b Serviço de Transplantação de Medula Óssea, Instituto Português de Oncologia do Porto, Porto, Portugal

ARTICLE INFO

Article history:

Received 24 March 2021

Accepted 10 June 2021

Available online 29 October 2021

Keywords:

Hematopoietic stem cell transplantation
Acute kidney injury
Mortality

ABSTRACT

Introduction and objectives: Acute kidney injury (AKI) is a frequent complication of hematopoietic stem cell transplantation (HSCT) and appears to be linked to increased morbidity and mortality. The aim of this study was to evaluate the incidence, etiology, predictors and survival impact of early AKI in the post-allogeneic HSCT setting.

Patients and methods: We performed a retrospective single center study that included 155 allogeneic transplant procedures from June 2017 through September 2019.

Results: AKI was observed in 50 patients (32%). In multivariate analysis, age (OR 31.55, 95% CI [3.42; 290.80], $p=0.002$), evidence of disease at the time of transplant (OR 2.54, 95% CI [1.12; 5.75], $p=0.025$), cytomegalovirus reactivation (OR 5.77, 95% CI [2.43; 13.72], $p<0.001$) and hospital stay >35 days (OR 2.66, 95% CI [1.08; 6.52], $p=0.033$) were independent predictors for AKI. Increasing age (HR 1.02, 95% CI [1.00; 1.04], $p=0.029$), increasing length of hospital stay (HR 1.02, 95% CI [1.01; 1.03], $p=0.002$), matched unrelated reduced intensity conditioning HSCT (HR 1.91, 95% CI [1.10; 3.33], $p=0.022$), occurrence of grade III/IV acute graft-versus-host disease (HR 2.41, 95% CI [1.15; 5.03], $p=0.019$) and need for mechanical ventilation (HR 3.49, 95% CI [1.54; 7.92], $p=0.003$) predicted an inferior survival in multivariate analysis. Early AKI from any etiology was not related to worse survival.

Conclusion: Patients submitted to HSCT are at an increased risk for AKI, which etiology is often multifactorial. Due to AKI incidence, specialized nephrologist consultation as part of the multidisciplinary team might be of benefit.

© 2021 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IQR, interquartile range; MAC, myeloablative conditioning regimen; MRD, measurable residual disease; MUD, matched unrelated donor; MV, mechanical ventilation; RIC, reduced intensity conditioning regimen; SOS, sinusoidal obstruction syndrome; TA-TMA, transplantation-associated thrombotic microangiopathy.

* Corresponding author.

E-mail address: mariamarmenezes@gmail.com (M.d.M. Menezes).

<https://doi.org/10.1016/j.nefro.2021.06.010>

0211-6995/© 2021 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Lesión renal aguda después de trasplante de células madre hematopoyéticas alogénicas, factores predictivos e impacto en la supervivencia: un estudio retrospectivo en un solo centro

R E S U M E N

Palabras clave:

Trasplante de células madre hematopoyéticas
Lesión renal aguda
Mortalidad

Introducción y objetivos: La lesión renal aguda (LRA) es una complicación frecuente del trasplante de células madre hematopoyéticas (TCMH) y parece estar asociado a un incremento en la morbilidad y la mortalidad. El objetivo de este estudio fue evaluar la incidencia, la etiología, los factores predictivos y el impacto en la supervivencia de la LRA temprana en el contexto posterior al TCMH alogénico.

Pacientes y métodos: Se realizó un estudio retrospectivo en un único centro que incluyó 155 procedimientos de trasplante alogénico desde junio de 2017 hasta septiembre de 2019.

Resultados: Se observó LRA en 50 pacientes (32%). En el análisis de múltiples variables, la edad (OR 31,55, IC del 95% [3,42; 290,80], $p=0,002$), la evidencia de enfermedad en el momento del trasplante (OR 2,54, IC del 95% [1,12; 5,75], $p=0,025$), reactivación de citomegalovirus (OR 5,77, IC del 95% [2,43; 13,72], $p<0,001$) y estancia hospitalaria > 35 días (OR 2,66, IC del 95% [1,08; 6,52], $p=0,033$) fueron los factores predictivos independientes para LRA. La mayor edad (HR 1,02, IC del 95% [1,00; 1,04], $p=0,029$), la mayor duración de la estancia hospitalaria (HR 1,02, IC del 95% [1,01; 1,03], $p=0,002$), TCMH con acondicionamiento de intensidad reducida no relacionados emparejados (HR 1,91, IC del 95% [1,10; 3,33], $p=0,022$), aparición de enfermedad injerto contra huésped aguda de grado III/IV (HR 2,41, IC del 95% [1,15; 5,03], $p=0,019$) y necesidad de ventilación mecánica (HR 3,49, IC del 95% [1,54; 7,92], $p=0,003$) predijeron una supervivencia inferior en el análisis de múltiples variables. La LRA temprana de cualquier etiología no se asoció con una peor supervivencia. **Conclusión:** Los pacientes sometidos a TCMH presentan un mayor riesgo de LRA, cuya etiología es con frecuencia multifactorial. Debido a la incidencia de LRA, la consulta a un nefrólogo especializado como parte del equipo multidisciplinario podría ser beneficiosa.

© 2021 Sociedad Española de Nefrología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Hematopoietic stem cell transplantation (HSCT) is increasingly used to treat several malignant and non-malignant hematologic diseases and some solid neoplasms. Acute leukemia represents more than 50% of allogeneic transplant indications, while lymphoproliferative disorders and multiple myeloma are the most frequent for autologous transplants.^{1–3}

The allogeneic HSCT procedure is complex and the selection of conditioning regimen, either myeloablative (MAC) or of reduced intensity (RIC), type of donor, and stem cell source all influence the expected outcome.^{1,4}

Both acute kidney injury (AKI) and chronic kidney disease (CKD) are described as frequent complications of HSCT and they appear to be linked to increased morbidity and mortality.^{5,6}

The incidence of AKI depends on the type of HSCT, conditioning regimen and the definition used to classify AKI, and usually occurs within the first 100 days after transplantation. While AKI incidence ranges from 10% to 20% in autologous HSCT, it can vary from 50% in RIC to 75% in MAC allogeneic transplants. Timing and severity of AKI appear to correlate with mortality, and the need for dialysis results in a bad outcome (mortality rate of 80–100%).^{7–10} Therefore, efforts have been made to identify, prevent and treat AKI early.

The etiology of AKI after allogeneic HSCT can be divided into three categories for better understanding: pre-renal, renal, and post-renal (obstructive). Pre-renal causes include mainly dehydration due to GI losses and mucositis. Renal causes encompass glomerular affections like transplantation-associated thrombotic microangiopathy (TA-TMA); acute tubular necrosis (ischemic and/or toxic) due to sepsis, septic shock, and dimethyl sulfoxide toxicity from cryopreserved stem cells; and acute interstitial nephritis induced by drugs or opportunistic infections like BK virus or adenovirus. Obstructive causes may be intratubular (e.g. acyclovir) or postrenal secondary to retroperitoneal fibrosis, lymphadenopathy, or hemorrhagic cystitis due to BK or adenovirus.¹⁰

The aim of this study was to evaluate the incidence, etiology, predictors and survival impact of AKI in the post-allogeneic HSCT setting.

Material and methods

Study design and patient selection

This was a retrospective cohort single center study. All allogeneic transplant procedures from June 2017 through September 2019 were included, with data collection until

September 2020. Median follow-up was 17 months (interquartile range, IQR, 8.1–25.9 months).

Data collection

All data were collected retrospectively from the patients' medical records. Demographic and clinical data included: age, gender, significant past medical history of arterial hypertension, diabetes mellitus and CKD; basal kidney function characterization by estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for adults or Revised Schwartz equation for children/adolescents, measured GFR with EDTA test when available and proteinuria; previous hematological diagnosis/indication for HSCT; more than 3 previous lines of treatment; disease status pre-HSCT; donor characteristics, source and cryopreservation of hematopoietic progenitor cells; conditioning regimen; GvHD prophylaxis; days of hospitalization; occurrence of early complications post-HSCT (infection, use of antibiotics, antivirals and antifungals, acute GvHD, sinusoidal obstruction syndrome (SOS), TA-TMA, intensive care unit (ICU) admission, need for mechanical ventilation (MV); AKI in the first 100 days post-HSCT, its' etiology and need for renal replacement therapy. We also documented the eGFR, proteinuria and albuminuria at 30 days, 100 days and one-year post-HSCT.

AKI is defined according to the KDIGO classification system¹¹ as an abrupt decrease in kidney function

occurring over 7 days or less. It can be further divided into 3 stages according to the severity of increase of baseline creatinine values. CKD is defined as a measured or estimated GFR <60 ml/min/1.73 m², or the presence of markers of kidney damage (e.g., albuminuria) for >90 days.¹¹

Since not all patients had GFR measured by EDTA, we chose to use eGFR calculated by CKD-EPI formula to allow comparison between groups.

Follow-up was considered until last observation or death during the data collection period.

Statistical analysis

Association between each study variable and AKI was first explored using chi-square and Fisher's exact test for categorical variables. Univariate logistic regression model was used next to determine which variables could be of interest.

Survival curves for mortality were obtained with the Kaplan–Meier method and univariate Cox regression model was used to determine which variables could be of interest as predictors of long-term mortality.

Multivariate analysis was performed to determine the independent predictors of AKI, adjusting a logistic regression model, and to determine the predictors of mortality, adjusting a Cox regression model. All statistically significant variables in the univariate analysis and those considered clinically relevant were included.

Table 1 – Patients' baseline characteristics.

Patient characteristics	Children/adolescents	Adults
N (%)	19 (12.3)	136 (87.7)
Female gender, N (%)	9 (47)	65 (47)
Age (years)		
Range	0–15	19–66
Mean ± SD	5.7 ± 4.6	44.3 ± 13.3
Glomerular filtration rate (CKD-EPI)		
Mean ± SD (mL/min/1.73 m ²)	188.4 ± 65.8	105.9 ± 19.8
Glomerular filtration rate (EDTA)		
Mean ± SD (mL/min/1.73 m ²)	143.1 ± 62.4	98.6 ± 28.6
Previous diagnosis (N)	Primary immunodeficiency (5) Acute lymphoblastic leukemia (4) Fanconi Anemia (4) Others (6)	Acute myeloid leukemia (45) Acute lymphoblastic leukemia (20) Myelodysplastic syndrome (17) Hodgkin lymphoma (10) Aplastic Anemia (8) Primary myelofibrosis (8) Non-Hodgkin lymphoma (6) Others (26)
Evidence of complete response pre-transplant (with MRD negative, when appropriate), N (%)	6 (31.6)	66 (48.5)
Comorbidities, N (%)		
Arterial hypertension	None	9 (6.6)
Diabetes mellitus	None	5 (3.7)
Chronic kidney disease	None	2 (1.5)
Proteinuria	None	9 (11.7) (missing 59)
More than 3 previous lines of treatment	None	15 (11)

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; EDTA – ethylenediamine tetraacetic acid; MRD – measurable residual disease.

Table 2 – Transplant procedure characteristics and frequency of early complications.

Transplant procedure characteristics	N (%)
Total	155 (100)
<i>Donor</i>	
Matched related donor	55 (35.5)
MUD	98 (63.2)
Haploidentical	2 (1.3)
<i>Source of hematopoietic progenitors</i>	
Peripheral blood	130 (83.9)
Bone marrow	23 (14.8)
Cord blood	2 (1.3)
<i>Cryopreserved hematopoietic progenitors</i>	17 (11)
<i>Myeloablative conditioning</i>	82 (52.9)
<i>GvHD prophylaxis</i>	
Containing cyclosporine	63 (40.6)
Containing tacrolimus	90 (58.0)
Containing methotrexate	67 (43.2)
Transplant procedure complications	
<i>Infectious complications</i>	
Febrile syndrome	121 (78.1)
Viral reactivation (serum)	49 (31.6)
Cytomegalovirus (CMV)	42
Adenovirus	2
BK polyomavirus	2
CMV + adenovirus	1
CMV + BK polyomavirus	2
Viral reactivation (urine)	19 (12.3)
BK polyomavirus	17
Adenovirus	1
BK polyomavirus + adenovirus	1
<i>Acute GvHD</i>	
Global grade \geq II	54 (34.8)
Sinusoidal obstruction syndrome	9 (5.8)
Transplant-associated thrombotic microangiopathy	6 (3.9)

CMV – Cytomegalovirus; GvHD – graft-versus-host disease; MUD – matched unrelated donor.

Results are expressed as odds ratios (OR) for all logistic regression models and as hazard ratios (HR) for all Cox regression models, both with 95% confidence intervals (95%CI). A *p*-value of <0.05 was considered statistically significant. All analyses were performed using R statistical software (version 4.0.3).

Results

Patient characteristics

During the study period, 155 patients were transplanted, whose main characteristics are presented in Table 1. Most patients were adults without significant comorbidities, and acute myeloid leukemia was the most common indication for HSCT.

HSCT characteristics and complications

The characterization of the HSCT procedures and the main complications in the early post-HSCT period are presented in Table 2.

More than 60% of the HSCT performed were from a matched unrelated donor (MUD), and peripheral blood was the most frequent graft source (83.9%). Only a minority of HSCT used cryopreserved hematopoietic stem cells (11%). The median length of hospital stay for the transplant procedure was 28 days (IQR 23–35), with a maximum of 175 days.

During the early post-transplant period, 121 (78.1%) patients had a documented febrile syndrome. The most frequent class of antibiotics used was beta-lactam antibiotics (*n* = 116). Fifty-six patients (36%) received more than one antibiotic either sequentially or in combination. Antifungal therapy was used in 50 patients (32%), most frequently caspofungin (*n* = 39) and liposomal amphotericin-B (*n* = 25). Antiviral therapy was initiated in 45 patients (29%), 12 of which received more than one agent. Ganciclovir/Valganciclovir was the most used antiviral (*n* = 39), followed by foscarnet (*n* = 13).

Acute GvHD was observed in a total of 62 patients (40%), of which 54 had grade II or higher acute GvHD (41, 7 and 6 with grades II, III and IV, respectively). SOS and TA-TMA were relatively rare complications. Fourteen patients (9%) were admitted to ICU in the early post-transplant period.

Kidney evaluation in the post-HSCT period

Regarding kidney evaluation of our sample, we verified that the median eGFR was similar at 30 days, 100 days and one year after transplant: 99 (IQR 76–116), 100 (IQR 77–116) and 103 (IQR 85–115) ml/min/1.73 m² among adults, respectively, and 127 (IQR 106–165), 141 (IQR 121–192) and 118 (IQR 106–156) ml/min/1.73 m² among children/adolescents, respectively). At one-year post-HSCT, only two adult patients had CKD criteria.

Adult patients had a median proteinuria of 133 mg/24 h (IQR 77–367) and 123 mg/24 h (IQR 72–347) at 30 days and 100 days post-HSCT, respectively. Median albuminuria at these time points was 22.7 mg/24 h (IQR 11.4–107.2) and 11 mg/24 h (IQR 5.8–27.0), respectively. However, there were many missing data regarding evaluation of albuminuria and proteinuria (e.g. at 30 days, no value was observed in 140 patients (18 children and 122 adults)). Therefore, these results must be interpreted with caution.

Acute kidney injury in the early post-HSCT setting

AKI was observed in 50 patients (32%) during the first 100 days post-transplant. We identified 30 patients in KDIGO AKI stage I, 12 in stage II and 8 in stage III. Only six patients were evaluated (and oriented) by a Nephrologist, all of whom needed renal replacement therapy, either intermittent hemodialysis (*n* = 1) or continuous venovenous hemodiafiltration (*n* = 5). All six patients were admitted into the ICU, needed MV and died within the first three months post-transplant.

The etiology of AKI included drug nephrotoxicity, particularly from tacrolimus, valganciclovir, cidofovir and colistin (*n* = 13), sepsis/septic shock (*n* = 10), mainly pre-renal due to diarrhea, vomiting or mucositis (*n* = 8), BK hemorrhagic cystitis (*n* = 4), SOS (*n* = 2), urinary tract infection (*n* = 1) and TA-TMA (*n* = 1). Unfortunately, we were not able to determine the cause of AKI in 11 patients.

Table 3 – Variables significantly associated with AKI in univariate and multivariate analysis.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age						
Group 18–49 years vs group < 18 years	11.74	1.49; 92.61	0.019	31.55	3.42; 290.80	0.002
Group ≥50 years vs group < 18 years	8.34	1.04; 67.16	0.046	21.31	2.25; 201.90	0.008
Any evidence of disease pre-HSCT	2.43	1.19; 4.93	0.013	2.54	1.12; 5.75	0.025
CMV reactivation	5.67	2.67; 12.05	<0.001	5.77	2.43; 13.72	<0.001
Hospital stay ≥35 days	2.89	1.39; 6.06	0.004	2.66	1.08; 6.52	0.033
ICU admission	9.59	2.54; 36.22	<0.001			NS
MV	11.59	2.40; 55.98	<0.001			NS
Use of five classes of antibiotics (beta-lactam + carbapenem + aminoglycoside + vancomycin + quinolone)	7.02	1.36; 36.16	0.012			NS
Use of ganciclovir/valganciclovir	4.02	1.70; 9.52	0.003			NS
Use of at least one antiviral	3.05	1.44; 6.58	0.001			NS
Use of at least one antifungal	2.53	1.21; 5.38	0.007			NS
TA-TMA	11.44	1.30; 100.78	0.014			NS
GvHD prophylaxis with cyclosporine and MMF	0.42	0.18; 0.99	0.042			NS
Isolated beta-lactam antibiotic use	0.41	0.18; 0.95	0.035			NS

CMV – cytomegalovirus; GvHD – graft-versus-host disease; HSCT – hematopoietic stem cell transplant; ICU – intensive care unit; MMF – mycophenolate mofetil; MV – mechanical ventilation; NS – not significant; TA-TMA – transplant-associated thrombotic microangiopathy.

AKI predictors in the early post-HSCT setting

Variables significantly associated with AKI in the early post-transplant period in univariate and multivariate analysis are discriminated in Table 3. In univariate analysis, in contrast to most variables studied, GvHD prophylaxis with cyclosporine and mycophenolate mofetil (as used in matched related donor RIC HSCT) and isolated beta-lactam antibiotic use were associated with a lower AKI risk.

In multivariate analysis, only four variables remained as independent predictors for increased risk of AKI (Table 3): adult age (OR 31.55, 95%CI [3.42;290.8], $p=0.002$, and OR 21.31, 95%CI [2.25;201.9], $p=0.008$ for patients 18–49 years and ≥50 years, respectively), any evidence of disease pre-HSCT (OR 2.54, 95%CI [1.12;5.75], $p=0.025$), CMV reactivation (OR 5.77, 95%CI [2.43;13.72], $p<0.001$), and hospital stay longer than 35 days (OR 2.66, 95%CI [1.08;6.52], $p=0.033$).

Prognosis and survival analysis

With a median follow-up time of 17 months (IQR 8.1–25.9 months), 67 patients died, 28 of which in the ICU. The median overall survival was 29.6 months (95%CI [21.2; not reached], Fig. 1).

Significant results of univariate and multivariate analysis for survival after allogeneic HSCT are described in Table 4. In univariate analysis, a higher maximum serum creatinine at 30 days post-HSCT and the need for renal replacement therapy correlated with worse survival. However, overall survival was not significantly different between patients with or without documented AKI, despite a trend toward a worse prognosis in the first year (Fig. 1B).

In multivariate analysis, only increasing age (HR 1.02, 95%CI [1.00;1.04], $p=0.029$), increasing length of hospital stay (HR 1.02, 95%CI [1.01;1.03], $p=0.002$), MUD RIC HSCT (HR 1.91, 95%CI [1.10;3.33], $p=0.022$), occurrence of grade III/IV acute GvHD (HR 2.41, 95%CI [1.15;5.03], $p=0.019$) and the need for

MV (HR 3.49, 95%CI [1.54;7.92], $p=0.003$) predicted an inferior survival (Table 4). AKI from any etiology during the first 100 days post-transplant did not correlate with a worse survival.

Discussion

Allogeneic HSCT is a complex procedure that has been increasingly used as a curative approach for many malignant and non-malignant hematological diseases. The most frequent indications for HSCT in our population were in accordance with international data.³

AKI is a recognized complication in the HSCT setting and it may imply a worse prognosis.¹ It is often multifactorial and is more common in allogeneic than in autologous HSCT.^{1,5,12,13} The frequency of AKI observed in this study (32%) is in the lower range of that reported in the literature.^{1,14,15} No significant differences were seen between RIC or MAC regimens, in accordance with previous results.^{1,5,6,16} AKI etiology observed in our sample is also in agreement with other studies.¹⁰

Even though AKI was observed in 50 patients, only six had a Nephrologist consultation, which correspond to patients who needed dialysis. The high mortality in the dialysis group is in line with that previously reported.^{7–10} Twenty patients had an AKI KDIGO stage 2 or more, and therefore could have benefited from specialized support. Only two patients had documented CKD at one-year post-HSCT, none of whom with previously documented AKI, and one with known CKD pre-HSCT. Therefore, it was not possible to demonstrate the influence of early AKI in CKD development in this study. This might have been limited by missing albuminuria and proteinuria data (more than 77%), and a short follow-up time for CKD development.

Another limitation of this analysis is the fact that it is mostly based on serum creatinine values. Since patients frequently lose weight and muscle mass during the peri-HSCT period and their hydration status is not steady over time, these results may be misleading. Using Cystatin C (not available at the time) might have allowed a more accurate analysis.

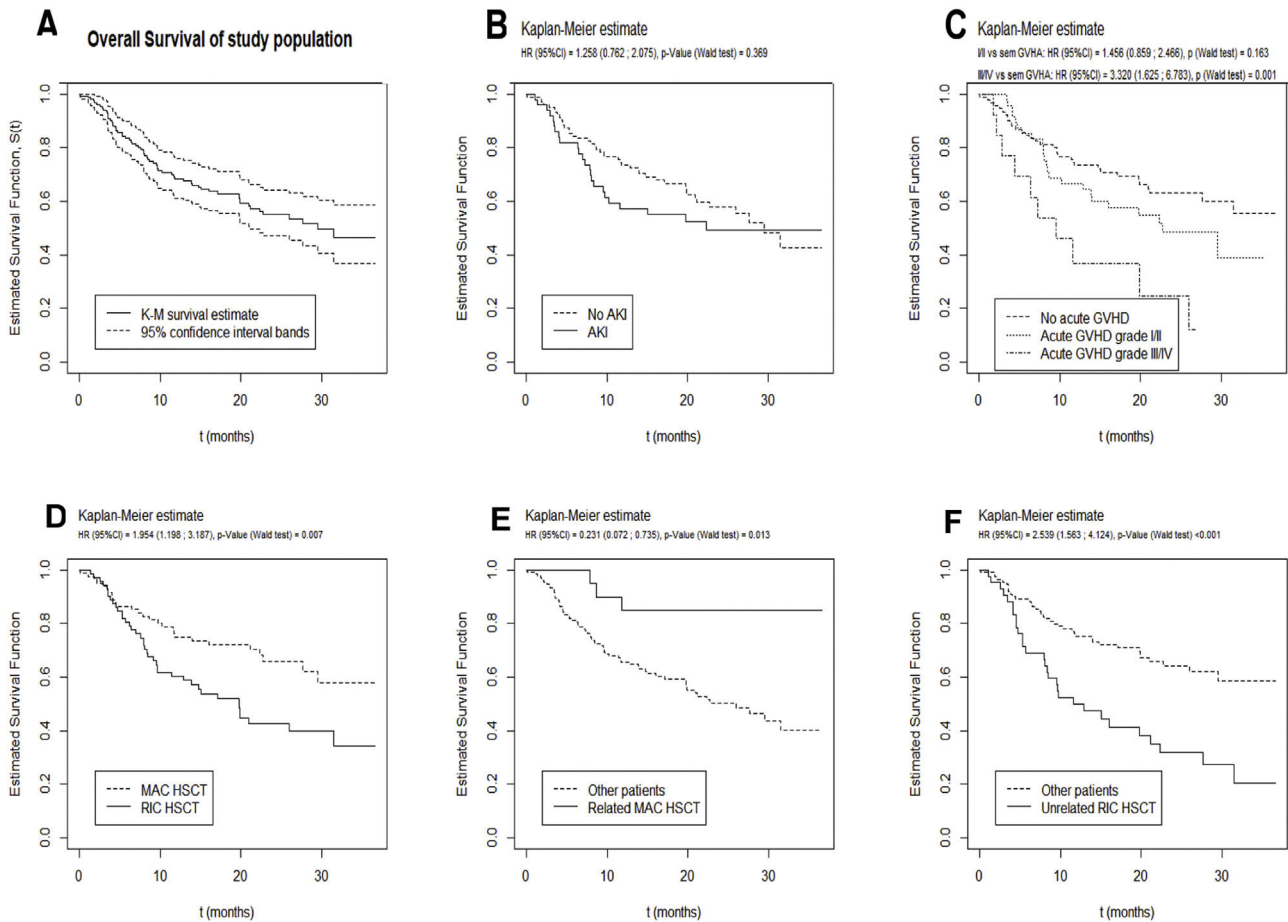


Fig. 1 – Overall survival of the entire study cohort (A) and according to the development of AKI post-HSCT (B), different grades of acute GvHD (C), type of conditioning regimen (D) and combination of type of donor and conditioning regimen (E, F).

In this study, we aimed to identify predictors of AKI in the post-HSCT period. In univariate analysis, we observed that patients between 18 and 49 years had the highest risk for AKI, which could be explained by a greater exposure to aggressive treatments as compared to older adults.

Variables that indirectly relate to worse clinical condition, such as a longer hospital stay, ICU admission, the need for MV, and use of antifungal, antiviral or more complex antibiotic therapy, correlated with an increased risk of AKI, as previously described in the literature.¹⁰ CMV reactivation is a potentially serious complication associated with the compromised immune function in the post-HSCT period, and could cause target organ disease and multiorgan dysfunction, including AKI.¹⁴ Antiviral treatment directed at CMV is also potentially nephrotoxic. TA-TMA is a recognized complication of HSCT due to endothelial damage by chemotherapy, GvHD, infection, and use of calcineurin inhibitors.¹⁷ The kidney is one of the most affected organs in TA-TMA due to its rich microvasculature and high blood supply, so its association with AKI was expected.

The use of cyclosporine per se was not related to AKI, despite theoretical implications related to its effects in renal perfusion besides its contribution in TA-TMA risk. Other studies also failed to find this correlation.^{1,4,14} Cyclosporine plus mycophenolate mofetil are given as GvHD prophylaxis to the

patients submitted to a matched related donor RIC HSCT. They are usually exposed to lower intensity drugs and have a lower risk of overall complications, which might help to explain why these patients have a smaller risk of AKI. Infectious complications that are treated with only a beta-lactam antibiotic (the first antibiotic empirically used when febrile complications arise) are more likely to have no major complications and a more rapid discharge from hospital, hence the correlation with a lower risk of AKI.

In multivariate analysis, only four of these variables independently predicted an increased risk of AKI during the early post-transplant period: adult age, any evidence of disease pre-HSCT, CMV viremia, and prolonged hospital stay. These may reflect an increased susceptibility to AKI, due to worse clinical condition and/or exposure to more potentially nephrotoxic drugs.

Regarding mortality predictors, we found that patients who had a RIC HSCT had a higher probability of worse survival than patients who received a MAC regimen, particularly if from a MUD. The nature of this study does not allow to clarify these results, but it is possible that this relates to older age, greater comorbidity load or greater risk of relapse of patients who receive a RIC, as opposed to a greater transplant-related mortality expected with a MAC regimen. Development of GvHD is more probable in MUD HSCT, which could also contribute to

Table 4 – Variables significantly associated with survival after allogeneic HSCT in univariate and multivariate analysis.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	HR	95% CI	p-value
<i>Patient characteristics</i>						
Age ≥50 years vs <50 years (continuous variable)	1.66	1.03; 2.69	0.038	1.02	1.00; 1.04	0.029
<i>HSCT characteristics</i>						
Non-MAC vs MAC	1.95	1.20; 3.19	0.007			NS
Composite MAC/related donor	0.23	0.07; 0.74	0.013			NS
Composite RIC/unrelated donor	2.54	1.56; 4.12	<0.001	1.91	1.10; 3.33	0.022
Hospital stay (continuous variable)	HR 1.02	1.01; 1.03	0.001	1.02	1.01; 1.03	0.002
<i>Complications post-HSCT</i>						
CMV reactivation	2.38	1.43; 3.95	0.001			NS
Any Acute GvHD	1.74	1.07; 2.81	0.024			NS
Acute GvHD Grade III/IV vs no GvHD or grades I/II	2.87	1.46; 5.65	0.002	2.41	1.15; 5.03	0.019
TA-TMA	5.07	1.97; 13.0	0.001			NS
ICU admission	8.97	4.75; 16.95	<0.001			NS
Mechanical ventilation	8.59	4.34; 17.01	<0.001	3.49	1.54; 7.92	0.003
<i>Antimicrobial therapies</i>						
Use of five classes of antibiotics (beta-lactam + carbapenem + aminoglycoside + vancomycin + quinolone)	4.11	1.82; 9.23	0.001			NS
Therapy with at least one antiviral	2.30	1.42; 3.73	0.001			NS
Maximum serum creatinine at 30 days post-HSCT (continuous variable)	HR 1.66	1.17; 2.37	0.005			NS
Renal replacement therapy	20.3	6.99; 58.85	<0.001			NS

CKD – chronic kidney disease; GvHD – graft-versus-host disease; HSC – hematopoietic stem cells; ICU – intensive care unit; MAC – myeloablative conditioning; MUD – matched unrelated donor; RIC – reduced intensity conditioning; SOS – sinusoidal obstruction syndrome; TA-TMA – transplant-associated microangiopathy.

these findings. MUD RIC HSCT remained as an independent predictor of mortality in the multivariate model.

It is not unexpected that patients who experience serious early complications of HSCT, such as severe infection, TA-TMA or severe acute GvHD (indirectly represented by a longer hospital stay, more complex antibiotic regimens, ICU admission, need for organ support such as MV), have a worse outcome, as shown in the univariate analysis. CMV reactivation related to a worse survival, as expected.¹⁸ Increasing age at the time of HSCT also related to worse outcomes. In multivariate analysis, only age, length of hospital stay, the need for MV and grade III/IV acute GvHD remained as independent predictors of mortality, probably representing patients with more severe clinical condition.

Previous studies support that AKI correlates with a worse survival in the post-HSCT setting^{15,18–20} and this could be more significant for more severe or earlier (pre-engraftment) AKI.^{7,15,16} Our results, however, did not support those findings. This could be due to the method used to determine the presence of AKI (serum creatinine), lack of albuminuria data, which is a recognized marker of kidney injury, a predictor of CKD and is associated with increased mortality,¹ or relatively short follow-up time compared to other studies. AKI in allogeneic transplanted patients could be more frequently a consequence of an underlying acute condition such as GvHD or severe bacterial, fungal or viral infection, and therefore not an independent predictor of mortality. Dialysis requirement correlated with a high mortality, as described in the literature,⁷ but only in univariate analysis, perhaps due to its occurrence in only six patients.

This study has limitations, particularly due to its retrospective nature. Besides, it is sometimes difficult to determine the confounding or overlapping effect of some of the variables analyzed. Nevertheless, this study collects a relevant sample of HSCT procedures. Although the follow-up time is not very long, it allows for an analysis of early AKI development and related outcomes.

Conclusions

Patients submitted to HSCT are at an increased risk for AKI, not only due to exposure to many potentially nephrotoxic drugs, but also to the risk of complications such as sepsis, GvHD, CMV disease, SOS and TA-TMA, so they could benefit from specialized Nephrologist consultation as part of the multidisciplinary team. Although previous studies have reported decreased survival associated with AKI, we could not demonstrate a survival impact of AKI development in the early post-HSCT period. In the future, it would be interesting to evaluate prospectively the underlying causes, timing and impact of AKI development in the peri-HSCT period.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None declared.

Acknowledgements

We thank Adriana Belo for her contribution with the statistical analysis.

REFERENCES

- Hingorani S. Renal complications of hematopoietic-cell transplantation. *N Eng J Med*. 2016;374:2256–67.
- Sawinski D. The kidney effects of hematopoietic stem cell transplantation. *Adv Chronic Kidney Dis*. 2014;1:96–105.
- Passweg J, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40000 transplants annually. *Bone Marrow Transplant*. 2016;51:786–92.
- Renaghan A, Jaimes E, Malyszko J, Perazella M, Sprangers B, Rosner M. Acute kidney injury and CKD associated with hematopoietic stem cell transplantation. *Clin J Am Soc Nephrol*. 2020;15:289–97.
- Angelo J, Hingorani S. Hematopoietic stem cell transplant-related kidney disease. *American Society of Nephrology*; 2016 [chapter 9]. <https://www.asn-online.org/education/distancelearning/curricula/onco/Chapter9.pdf> [accessed 1 December 2020].
- Negrin R. Kidney disease following hematopoietic cell transplantation. *Uptodate*; 2018. <https://www.uptodate.com/contents/kidney-disease-following-hematopoietic-cell-transplantation> [accessed 1 January 2021].
- Hahn T, Rondeau C, Shaikat A, Jupudy V, Miller A, Alam AR, et al. Acute renal failure requiring dialysis after allogeneic blood marrow transplantation identifies very poor prognosis patients. *Bone Marrow Transplant*. 2003;32, 405–140.
- Mima A, Tansho K, Nagahara D, Tsubaki K. Incidence of acute kidney disease after receiving hematopoietic stem cell transplantation: a single-center retrospective study. *PeerJ*. 2019;7:e6467, <http://dx.doi.org/10.7717/peerj.6467>.
- Krishnappa V, Gupta M, Manu G, Kwatra S, Owusu O. Acute kidney injury in hematopoietic stem cell transplantation: a review. *Int J Nephrol*. 2016, <http://dx.doi.org/10.1155/2016/5163789>. Epub ahead of print.
- Lopes JA, Jorge S. Acute kidney injury following HCT: incidence, risk factors and outcome. *Bone Marrow Transplant*. 2011;46:1399–408.
- Ostermann M, Bellomo R, Burdmann E, Winkelmayr W, Kellum J. Controversies in acute kidney injury: conclusions from a kidney disease: improving Global Outcomes (KDIGO) Conference. *Kidney Int*. 2020;98:294–309.
- Ando M. An overview of kidney disease following hematopoietic cell transplantation. *Inter Med*. 2018;57:1503–8.
- Ellis MJ, Parikh CR, Inrig JK, Kambay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: a systematic review. *Am J Transplant*. 2008;8:2378–90.
- Madsen K, Cote G, Pelletier K, Kitchlu A, Chen S, Mattsson J, et al. Incidence, outcomes and predictors of acute kidney injury post allogeneic stem cell transplant. *Blood*. 2020;136(S1):16–7.
- Khalil A, Khalil L, Awidi A. Incidence, risk factors and prognosis of acute kidney injury following hematopoietic stem cell transplant: a pilot study. *Int J Stem Cells*. 2019;12:43–50.
- Shingai N, Morito T, Najima Y, Kobayashi T, Doki N, Kakihana K, et al. Early-onset acute kidney injury is a poor prognostic sign for allogeneic SCT recipients. *Bone Marrow Transplant*. 2015;50:1557–62.
- Khosla J, Yeh A, Spitzer T, Day B. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: current paradigm and novel therapies. *Bone Marrow Transplant*. 2018;58:129–37.
- Gutiérrez-García G, Villarreal J, Garrote M, Rovira M, Blasco M, Suárez-Lhedo M, et al. Impact of severe acute kidney injury and chronic kidney disease on allogeneic hematopoietic cell transplant recipients: a retrospective single center analysis. *Bone Marrow Transplant*. 2020;55:1264–71.
- Parikh CR, McSweeney P, Schrier RW. Acute renal failure independently predicts mortality after myeloablative allogeneic hematopoietic cell transplant. *Kidney Int*. 2005;67:1999–2005.
- Sakaguchi M, Nakayama K, Yamaguchi H, Mii A, Shimizu A, Inai K, et al. Risk factors for acute kidney injury and chronic kidney disease following allogeneic hematopoietic stem cell transplantation for hematopoietic malignancies. *Acta Haematol*. 2020;143:452–64.