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Universidade de Lisboa

Faculdade de Medicina

Epidemiologic evaluation of Acute Kidney Injury in hemato-oncologic patients

Avaliação epidemiológica da Lesão Renal Aguda no doente hemato-oncológico

Natacha Jardim Rodrigues

Orientador: Prof. Doutor José António Lopes

Tese especialmente elaborada para obtenção do grau de Doutor em Medicina, especialidade Nefrologia

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2024

O trabalho aqui apresentado foi realizado no Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, EPE, com a colaboração do Departamento de Nefrologia e Transplantação Renal e do Departamento de Hematologia e Transplante de Medula.

I know I am talking nonsense, but I'd rather go rambling on, and partly expressing something I find it difficult to express, than to keep on transmitting faultless platitudes.

— Thomas Mann, The Magic Mountain

We should be taught not to wait for inspiration to start a thing. Action always generates inspiration. Inspiration seldom generates action.

- Frank Tibolt

The greatest challenge to any thinker is stating the problem in a way that will allow a solution

– Bertrand Russell

Para os meus doentes, o meu motivo.

Para os meus pais e o meu irmão, as minhas raízes.

Para o Martim e o Tomás, o meu sorriso.

Preface

In 2006, I was invited to collaborate with the biochemistry department of the Integrated Master Degree in Medicine at the Nova Medical School of Universidade Nova de Lisboa directed by Prof. Armando Sena while I was a second-year student at this institution. During this collaboration, I monitored four classes per year, corresponding to three hours a week, and I collaborated with the clinical research taking place in this department for four years. This experience resulted in my first interest in the academic and clinical investigation fields.

When I graduated in 2012, I chose a department with a reputation for high clinical quality and consistent contribution to clinical investigation in a university hospital - the Department of Nephrology and Renal Transplantation of Centro Hospitalar Universitário Lisboa Norte, EPE (CHULN, EPE) – for my nephrology residency. I had the opportunity to start working closely with Prof. José Antonio Lopes - head of this department, head the Nephrology Unit at Faculty of Medicine of the University of Lisbon and editor-in-chief of the Portuguese Journal of Nephrology and Hypertension - in his many studies on Acute Kidney Injury, which played a preponderant role in my decision to enroll in the research field. Also, during my residency, I had the opportunity to do two internships abroad. Firstly, in 2015 in Hospital do Rim in São Paulo under the orientation of Prof. Medina Pestana, where all the clinicians had to apply to a post-graduation project as a requirement to work in that institution.This contact allowed me to understand and value the clinical research performed during clinical activity on a large scale. Secondly, in 2016 in Barcelona under the orientation of Prof. José Ibeas, where I also met Prof. Jordi Bover, who has an intensive clinical research experience on chronic kidney disease - metabolic bone disease, who has helped and encouraged me to develop research skills and has invited me several times to collaborate with his work in the past few years.

In 2017, my first year as an assistant nephrologist, I was assigned to do intra-hospital nephrology consultation. During the week, I was responsible for providing the nephrology assistance needed outside the department of nephrology. This

assignment put me in contact for the first time not only with patients with solid and hematologic malignancies facing acute or chronic renal complications related to the diagnosis or treatment but also with chronic kidney disease patients facing a new oncologic diagnosis and related challenges concerning their limited therapeutic options. I must say this new emerging field of onconephrology fascinated me by its novelty and complexity, putting me as a nephrologist outside my comfort zone. Amongst these patients, a particular population caught my attention: patients with hematologic malignancies undergoing hematopoietic stem cell transplant, a procedure performed in CHULN, EPE by the Department of Hematology and Bone Marrow Transplantation.

In 2019, I shared with Prof. José António Lopes my interest and desire to develop clinical research in this field in order to provide more knowledge that could be translated into better clinical care for our patients. The moment he accepted to guide me through the project that gave origin to this dissertation was one of great happiness and gratitude. We decided to perform an epidemiologic evaluation of AKI in hemato-oncologic patients – incidence, risk factors, prognostic impact - considering an updated definition of AKI. I submitted this project for the doctoral program at Lisbon Academic Medical Center, and it was accepted. In 2020 I was accepted to the Harvard Medical School Portugal Clinical Scholars Training Program, a two-year program where I acquired most of my skills for this clinical research.

These four years were intellectually and emotionally very challenging. I struggled with the constraints of the COVID pandemic, as it was extremely difficult to have access to the handwritten files needed for data collection and to meet with other collaborators or consultants. At the same time, clinical work increased significantly during this period compromising the time available for the Harvard Medical School Portugal Clinical Scholars Training program and for the research itself. Still, I believe I was able to develop my research skills, mature my scientific thinking, and improve my ability to design and develop scientific projects. Also, I consider this research to have an important impact on clinical practice.

As a clinician and a researcher, I aim to continue my investigation on onconephrology. I have started an onconephrology unit in my department with the support of Prof. José António Lopes and I hope to continue developing clinical and research work in this field.

Thesis outline

This dissertation focuses on Acute Kidney Injury (AKI) in hemato-oncologic patients undergoing hematopoietic stem cell transplant (HSCT) and aims to provide new insights on this matter by studying AKI incidence in this population using KDIGO classification with both creatinine and urinary output criteria, by identifying patients at risk, by determining the prognostic impact of AKI in this population, and by proposing a new predictive risk score for the development of this clinical situation.

The first chapter is dedicated to the introduction, where we provide an overview of hematopoietic stem cell transplantation, followed by an overview of AKI in general, and we finish with the current knowledge of AKI in patients undergoing HSCT. In the second chapter, we present our study questions and our aims according to each question. The third chapter describes the methodology used in the studies we performed in order to answer our questions. The fourth chapter presents our results and is subdivided into four categories – the first three categories are dedicated to specific populations (AKI in patients with Multiple Myeloma undergoing autologous HSCT, AKI in patients with Lymphoma undergoing autologous HSCT and AKI in patients with Leukemia undergoing allogeneic HSCT) and the last category concerns the predictive risk score for AKI in patients undergoing HSCT.

The fifth chapter is dedicated to the discussion, where we decided to approach each study question separately, contextualizing our results with the international literature and providing our future perspective.

The sixth and final chapter expresses our conclusions and final remarks, after which we mention our acknowledgements. All the papers are included as appendices.

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Summary

The incidence and prevalence of hematologic malignancies are increasing throughout the world. Hematopoietic Stem Cell Transplant (HSCT) is a potentially curative treatment for virtually all hematologic cancers, and the therapeutic benefits result from high-dose chemotherapy and the graft versus tumor effect that develops after allografting. With this epidemiologic increase, the overall number of patients requiring HSCT has also evolved, and the number of HSCTs performed has increased by 7% per year worldwide in the last five years. It is assumed that this trend will continue for the next several years. With this scenario arises the need to increase our knowledge on HSCT complications more than ever, and Acute Kidney Injury (AKI) occurring in the first 100 days after this procedure has been recently mentioned in the literature as a complication with an important prognostic impact.

AKI is a complex syndrome associated with numerous etiologies and pathophysiological mechanisms that lead to a rapid decrease in renal function. In the literature, we identify more than 35 different definitions for AKI. It was only in 2012 that the Kidney Disease Improving Global Outcomes (KDIGO) classification was proposed with the goal of standardizing the definition throughout the world to allow uniformization and consequently more coherent applicability in clinical practice, research, and public health fields. This classification takes into consideration two criteria—serum creatinine increases and urinary output decreases—and has three degrees of severity. AKI still does not have a specific treatment or prevention, and an early approach is still the best recommended attitude.

AKI in HSCT has been studied in the last decade, but the use of different AKI definitions, all based on serum creatinine changes, along with the inclusion of several hematologic diagnoses in the analyzed populations, has resulted in a wide range of results with no predictive risk score available.

The main objectives of this dissertation were 1) to evaluate the cumulative incidence, the earlier diagnosis criteria and severity of AKI according to KDIGO classification using both creatinine and urinary output criteria in the first 100 days

after HSCT in patients with multiple myeloma undergoing autologous HSCT, in patients with lymphoma undergoing autologous HSCT and in patients with leukemia undergoing allogeneic HSCT; 2) to define risk factors for AKI in each of the above mentioned populations; 3) to study the association of AKI with overall survival, relapse-free survival, and progression to chronic kidney disease in each of the above mentioned populations; 4) to calculate a predictive risk score for AKI considering variables available before the HSCT.

We conducted a single-center retrospective cohort study including 422 patients who were diagnosed with lymphoma, leukemia, or multiple myeloma and performed HSCT at our tertiary hospital between January 2005 and December 2015, and we considered a 5-year follow-up period. 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 those with previous HSCT. For our first three objectives, we analyzed our population separately according to the hematologic malignancy diagnosis and type of HSCT (patients with multiple myeloma undergoing autologous HSCT, patients with lymphoma undergoing autologous HSCT, and patients with leukemia undergoing allogeneic HSCT). For our last objective, we analyzed all patients. We followed the European Group for Blood and Marrow Transplantation guidelines on statistical methodology and used survival analysis methods considering competing events and addictive Cox proportional hazards regression models, backward stepwise regression to create the multivariable models, and the Liu index to establish the optimal cut-off for the clinical risk score.

The AKI cumulative incidence was 49.7% for patients with multiple myeloma undergoing autologous HSCT, 63.7% for patients with lymphoma undergoing autologous HSCT and 63.4% for patients with leukemia undergoing allogeneic HSCT. Urinary output reduction alone was the first AKI diagnostic criteria in 18.3% of AKI patients with multiple myeloma, in 41.1% of AKI patients with lymphoma, and in 15.4% of AKI patients. Considering the three study populations together, 24.9% of all AKI diagnoses were made first by a detectable urinary output reduction alone. In all subgroups, more than 80% of patients with AKI presented with AKI stage 1 on

the first day of AKI, but moderate-to-severe AKI was reached during the episode by 28.2% of AKI patients with multiple myeloma, 42.5% of AKI patients with lymphoma, and 38.6% of AKI patients with leukemia.

The most significant risk factors for AKI in patients with multiple myeloma were an Hematopoietic Cell Transplant comorbidity index (HCT-CI) score ≥ 2 points, mucositis grade 3–4, exposure to nephrotoxic drugs, a higher body mass index (BMI), chronic kidney disease (CKD), and the presence of amyloidosis. In patients with lymphoma, the most important risk factors for AKI were mucositis (any grade), exposure to nephrotoxic drugs, and an episode of shock. In patients with leukemia, the most important risk factors for AKI were an HCT-CI score ≥ 2 points, an episode of sepsis, previous exposure to radiotherapy, shock, and higher lactate dehydrogenase (LDH) levels the day before the conditioning regimen.

In patients with multiple myeloma undergoing autologous HSCT and patients with lymphoma undergoing autologous HSCT moderate to severe AKI was associated with a reduction in overall survival, and in patients with leukemia undergoing allogeneic HSCT this association was observed for patients who presented with severe AKI. No association was found between AKI in any stage and relapse-free survival, CKD progression, or eGFR reductions greater than 25%.

Our predictive risk score for AKI in patients with hematologic malignancies undergoing HSCT considers only inexpensive and easily accessed variables available before the procedure, including the presence of chronic kidney disease before HSCT, the HCT-CI score, the platelet-to-lymphocyte ratio at admission, and the hematologic malignancy diagnosis.

Although the retrospective single-center nature of our study limits its external validity, our results provide important knowledge on AKI in HSCT. It is the first study considering urinary output criteria for the AKI diagnosis in this population, which increased accuracy and showed a considerable percentage of cases in which this criterion alone is the first detectable change allowing earlier diagnosis and consequently earlier approach. Also, we analyzed for the first time AKI in patients with lymphoma undergoing autologous HSCT separately from other hematologic

diagnoses. By analyzing groups separately, we confirmed different risk factors for AKI according to the group of patients.

Although our score needs validation through multicenter prospective studies, we believe that a first and inexpensive predictive risk score for AKI in HSCT is crucial for a better AKI approach in this population.

Key words: Hematopoietic Stem Cell Transplant; Acute Kidney Injury; Epidemiology; Predictive Risk Score

Resumo

A nível mundial tem-se assistido a um aumento progressivo da incidência e prevalência de neoplasias hematológicas. O transplante de células hematopoiéticas é um procedimento potencialmente curativo para virtualmente todas as neoplasias hematológicas, estando os benefícios terapêuticos relacionados com a possibilidade de realizar quimioterapia em alta dose e com o efeito enxerto versus tumor. Com este aumento epidemiológico das neoplasias hematológicas, o número de doentes a beneficiar de transplante de células hematopoiéticas é crescente. O número de transplantes de células hematopoiéticas tem registado um aumento superior a 7% por ano nos últimos cinco anos em todo o mundo, sendo expetável que esta tendência se mantenha.

Este cenário remete-nos para a necessidade de estudar e compreender melhor as complicações associadas ao transplante de células hematopoiéticas. A Lesão Renal Aguda associada ao transplante de células hematopoiéticas ocorre nos primeiros 100 dias após este procedimento e tem sido, recentemente, apontada na literatura como uma complicação frequente e com importante impacto prognóstico a curto e longo prazo.

A Lesão Renal Aguda é uma síndrome complexa associada a inúmeras etiologias e resultante de vários mecanismos fisiopatológicos que levam a uma diminuição rápida da função renal. Existem na literatura mais de 35 definições para esta entidade e nesse contexto em 2012 a Kidney Disease Improving Global Outcomes (KDIGO) publicou a classificação KDIGO para a Lesão Renal Aguda. Os objetivos principais desta classificação foram o standardizar e uniformizar a aplicação da de uma única definição nos contextos da prática clínica, da investigação e da saúde pública. Esta classificação engloba dois critérios – o aumento da creatinina sérica e a redução do débito urinário - e contempla três graus de gravidade. A Lesão Renal Aguda ainda não tem um tratamento específico sendo que a prevenção e a deteção e abordagem precoces são as atitudes clínicas mais recomendadas.

A Lesão Renal Aguda no transplante de células hematopoiéticas tem sido estudada na última década mas a utilização de diferentes definições para Lesão Renal Aguda

- e todas baseadas apenas no aumento da creatinina sérica - bem como a inclusão de vários diagnósticos hematológicos nas populações dos estudos culminou numa inconsistência de resultados entre estudos. De facto, as incidências publicadas variam entre os 12 e os 80%. Não existe na literatura nenhum score de risco proposto para Lesão Renal Aguda no transplante de células hematopoiéticas.

Neste contexto, os objetivos principais desta dissertação são 1) avaliar a incidência cumulativa, os critérios de diagnóstico mais precoces e a gravidade da Lesão Renal Aguda - segundo a classificação KDIGO usando critério creatinina sérica e critério débito urinario nos primeiros 100 dias após transplante de células hematopoiéticas - em doentes com mieloma múltiplo submetidos a transplante de células hematopoiéticas autólogo, em doentes com linfoma submetidos a transplante de células hematopoiéticas autólogo e em doente com leucemia submetidos a transplante de células hematopoiéticas alogénico; 2) definir fatores de risco em cada uma das subpopulações mencionadas no ponto anterior; 3) estudar a associação entre a lesão renal aguda e a sobrevida geral, tempo livre de doença e a progressão para doença renal crónica em cada uma das subpopulações; 4) calcular um score preditivo de risco para lesão renal aguda considerando variáveis disponíveis antes da realização do procedimento.

Fizemos um estudo coorte unicêntrico retrospetivo que incluiu 422 doentes com o diagnóstico de linfoma, leucemia ou mieloma múltiplo que realizaram transplante de células hematopoiético num hospital terciário entre janeiro 2005 e dezembro 2015 e considerámos um tempo de *follow up* de cinco anos. Excluímos doentes com menos de 18 anos de idade, doentes com doença renal crónica já em terapêutica de substituição da função renal, doentes que realizaram terapêutica de substituição da função renal na semana anterior ao procedimento e doentes que já tivessem realizado pelo menos um transplante de células hematopoiéticas no passado.

Para os nossos três primeiros objetivos, analisámos a população separadamente de acordo com o diagnostico hematológico e tipo de transplante (doentes com mieloma múltiplo submetidos a transplante de células hematopoiéticas autólogo,

doentes com linfoma submetidos a transplante de células hematopoiéticas autólogo e em doente com leucemia submetidos a transplante de células hematopoiéticas alogénico). Para o nosso quarto objetivo analisamos todos os doentes em conjunto. Seguimos as linhas orientadoras demetodologia estatística do European Group for Blood and Marrow Transplantation - usámos métodos de análise de sobrevivência com eventos competitivos e modelos de regressão de risco proporcional de Cox e criamos os nossos modelos de análise multi-variável por regressão logística stewise backward. Usámos o Liu index para estabelecer o ponto de corte ótimo para o nosso score preditor de risco.

A incidência cumulativa de Lesão Renal Aguda foi de 49.7% nos doentes com mieloma múltiplo submetidos a transplante de células hematopoiéticas autólogo, de 63.7% nos doentes com linfoma submetidos a transplante de células hematopoiéticas autólogo e de 63.4% nos doentes com leucemia transplante de células hematopoiéticas alogénico.

A redução de débito urinário foi o primeiro critério para Lesão Renal Aguda a surgir isoladamente em 18.3% dos doentes com mieloma múltiplo que desenvolveram Lesão Renal Aguda, em 41.1% dos doentes com linfoma que desenvolveram Lesão Renal Aguda e em 15.4% dos doentes com leucemia que desenvolveram Lesão Renal Aguda. Em todos os subgrupos mais de oitenta por cento dos doentes com Lesão Renal Aguda presentaram-se no estadio 1 no primeiro dia de Lesão Renal Aguda mas o grau de moderado-a-grave foi atingido em 28.2% dos doentes com mieloma múltiplo, 42.5% dos doentes com linfoma e 38.6% dos doentes com leucemia.

Os fatores de risco mais importantes identificados no grupo de doentes com mieloma múltiplo foram um score no índice de comorbilidade do transplante de células hematopoiéticas igual ou superior a 2, mucosite grau 3-4, exposição a fármacos nefrotóxicos, Indice de Massa Corporal mais elevado, a presença de doença renal crónica e a presença de amiloidose No grupo de doentes com linfoma os fatores de risco mais importantes foram a mucosite (qualquer grau), a exposição a fármacos nefrotóxicos e episódio de choque. Nos doentes com leucemia os

fatores de risco identificados foram um score no índice de comorbilidade do transplante de células hematopoiéticas igual ou superior a 2, episódio de sépsis, exposição prévia a radioterapia, episodio de choque e níveis mais elevados de lactato desidronegase sérica no dia anterior ao dia do condicionamento.

Nos doentes com mieloma múltiplo submetidos a transplante autólogo e nos doentes com linfoma submetidos a transplante autólogo, a Lesão Renal Aguda moderada a grave esteve associada a uma redução da sobrevida global. Nos doentes com leucemia submetidos a transplante alogénico, esta associação foi estatisticamente significativa para a Lesão Renal Aguda grave. Não encontrámos nenhuma associação entre a Lesão Renal Aguda (qualquer grau de gravidade) e o tempo livre de doença nem com a progressão para doença renal crónica ou redução superior a 25% da taxa de filtração glomerular estimada.

O nosso score preditor de risco para Lesão Renal Aguda nos doentes com neoplasias hematológicas submetidos a transplante de células hematopoéticas - considerando variáveis de baixo custo e de fácil acesso disponíveis antes da realização do procedimento – leva em consideração a presença de doença renal crónica à data do transplante, o score obtido no índice de comorbilidade do transplante de células hematopoiéticas, a relação plaquetas/linfócitos à admissão hospitalar para o procedimento e o diagnóstico hematológico.

Apesar da natureza restrospetiva uni-cêntrica do nosso estudo limitar validação externa, consideramos que os nossos resultados aportam um contributo importante no estudo da Lesão renal Aguda no transplante de células hematopoiéticas. É o primeiro estudo a considerar o critério de débito urinário para o diagnostico de Lesão Renal Aguda nesta população - o que acreditamos aumentar a precisão diagnóstica - e permitiu perceber a percentagem considerável de casos nos quais este critério isoladamente é o primeiro a ser detetado podendo resultar num diagnóstico e consequentemente uma abordagem terapêutica mais precoces. Também analisámos pela primeira vez na literatura o grupo de doentes com linfoma submetidos a transplante autólogo separadamente dos outros diagnósticos hematológicos, sendo que mesmo os restantes subgrupos analisados

apresentavam muito poucos estudos prévios. Ao analisar os grupos separadamente confirmámos a presença de diferentes fatores de risco para Lesão Renal Aguda. Apesar do nosso score preditor de risco necessitar de mais validação através de estudos multi-cêntricos prospetivos, acreditamos que um primeiro score preditor de risco é mais um passo no caminho para uma melhor abordagem da Lesão Renal Aguda nesta população.

Palavras Chave: Transplante de células hematopoiéticas; Lesão Renal Aguda; Epidemiologia; Score preditor de risco

Abbreviations

ADQI	Acute Dialysis Quality Initiative group
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
AMR/PAH	Region of the Americas
BEAM	carmustine, etoposide, cytarabine and melphalan
BMI	Body Mass Index
CHULN,EPE	Centro Hospitalar Universitário Lisboa Norte, EPE
CKD	Chronic Kidney Disease
CI	Confidence interval
CMV	Cytomegalovirus
CML	Chronic Myeloid Leukemia
CR	Complete Remission
eGFR	Estimated Glomerular Filtration Rate
EBMT	European Bone Marrow Transplantation
EMR/AFR	Eastern Mediterranean/African Region
EUR	Europe
GVHD	Graft Versus Host Disease
HCT-CI	Hematopoietic Cell Transplant – Comorbidity Index
HSCT	Hematopoietic Stem Cell Transplant
HR	Hazard Ratio
HLA	Human Leukocyte Antigens
ICU	Intensive Care Unit
ISS	International Staging System
KDIGO	Kidney Disease Improving Global Outcomes
LDH	Lactate Dehydrogenase
MHC	Major Histocompatibility Complex
MDRD	Modification of Diet in Renal Disease

MDS	Myelodysplastic Syndrome
MPN	Myeloproliferative Neoplasm
RIC	Reduced-intensity Regimen
RIFLE	Risk Injury Failure Loss of Kidney Function End-stage Kidney Disease
SEAR/WPR	South-East Asia/ Western Pacific Region.
TMA/TLS/VOD	Thrombotic Microangiopathy, Tumor Lysis Syndrome or Veno-occlusive Disease.
TEAM	Thiotepa, Etoposide, Cytarabine and Melphalan
UO	Urine output
WHO	World Health Organization

Chapter 1 - Introduction

1.1 Hematopoietic Stem Cell Transplant

Historical background

In 1957, in New York, E. Donnell Thomas performed the first Hematopoietic Stem Cell transplant [1] between monozygotic twins to treat acute leukemia based on studies on the recovery of mice with bone marrow myelosuppression after infusion of healthy bone marrow components [2]. Although the first patients undergoing this procedure did not obtain successful results, in 1968 in Minnesota, the first successful allogeneic bone marrow transplant was made and involved a pediatric patient with severe combined immunodeficiency syndrome [3].

With increasing knowledge of the human major histocompatibility complex (MHC) genes encoding for human leukocyte antigens (HLA), matching for HLA and intense induction regimens resulted in initial survival; however, more than half of the patients would develop graft versus host disease (GVHD). Major improvements were reached when the combination of methotrexate and calcineurin inhibitors was used [4].

This procedure has evolved throughout the decades, and it is nowadays considered a potentially life-saving procedure and often the only curative option for a variety of diseases.

Characterization of the procedure

The rationale behind HSCT is the replacement of an unhealthy bone marrow and immune system with infused healthy stem cells and immune cells—the graft. This presupposes a previous course of chemotherapy, radiotherapy, or both—the conditioning regimen—to ablate the recipient's own bone marrow. The primary goal of most HSCT is to cure an underlying malignancy or hematologic disease.

The source of the graft can be peripheral blood, bone marrow, or umbilical cord units. Since the introduction of granulocyte colony-stimulating factor, most of the grafts are collected from peripheral blood through apheresis. Using peripheral blood

as a source has been related to faster recovery of the immune system, lower rates of failure, and a higher incidence of GVHD [5].

HSCT is generally classified according to the type of donor into:

- autologous: the stem cells are collected from the recipient and infused after high-dose chemotherapy with or without radiotherapy. This type of HSCT aims to allow the recovery of aplasia.
- allogeneic: the stem cells are collected from another individual, requiring a donor with acceptable HLA antigen compatibility, and this type of HSCT aims not only to allow recovery of aplasia but also to organize a graft-versus-tumor response [6].

The type of HSCT is chosen according to the best efficacy shown in clinical studies for each disease, and eligibility for HSCT implies not only the diagnosis but also the performance status of the individual, the exclusion of any active infection, and a mental health that allows the patient to cope with a period of intense therapy and follow-up. Also, depending on recipient age and fitness, the conditioning regimen can be myeloablative or non-myeloablative (also known as a reduced intensity regimen (RIC)).

Considering the need to induce a significant immunosuppressive state, a complex prophylactic approach is needed, including prophylaxis against bacterial infections, candidiasis, Pneumocystis jirovecci, the herpes virus, and GVHD [7].

Following the induction regimen and the graft infusion, blood counts are monitored daily, and when neutrophils reach a count greater than 0.5 x 10^9/L for three consecutive days, engraftment has occurred. In the pre-engraftment period, complications are related mainly to the conditioning regimen's toxicity: infections by gram-positive and gram-negative bacteria, the herpes simplex virus, candidiasis, and invasive aspergillosis [7]. The early post-engraftment period can be complicated not only with infection but also with syndromes related to endothelial injury and cytotoxin release, such as capillary leak syndrome, engraftment syndrome, veno-

occlusive disease, diffuse alveolar hemorrhage, and thrombotic microangiopathy. It is also the timing for acute GVHD [8].

In the late post-engraftment period, conceptually defined after the 100 days of transplant, complications include chronic GVHD in allogeneic HSCT, long-term side effects of immunosuppression and radiotherapy such as secondary cancers, organ-specific complications, late infections, quality of life impairments, psychosocial issues, and sexual and fertility concerns.

Indications and Epidemiology

Some solid tumors (especially germ cells, sarcomas, and neuroblastomas) might benefit from undergoing HSCT as part of rescue therapy [9-11] and HSCT can even be used in nonmalignant hematologic diseases such as sickle cell disease [12] or severe aplastic anemia [13], or certain metabolic disorders. However, this procedure is mainly performed on patients with hematologic malignancies. Acute leukemias are the most common indications for allogeneic HSCT [14]. Multiple Myeloma is the most common adult indication for autologous HSCT [14]. Relapsed / Refractory Hodgkin (HL) and non-Hodgkin Lymphomas (NHL) are the second most common adult indications for autologous HSCT [14] and their curability rates are high. The fact that increasing alkylating agent dosing can overcome the resistance of most lymphoma cells defines the biological rationale for the clinical use of autologous HSCT in second-line HL and NHL.

In the data presented in 2019 by the Worldwide Network for Blood and Marrow Transplantation (WBMT) [15], from 1957 to 2016, a total of 1,298,897 HSCT (57.1% autologous) procedures had been performed. HSCT activity has been reported in 87 of the 195 World Health Organization (WHO) member states. The global activity per year has been increasing continuously, from 10.000 per year in 1991 to 82,718 first HSCT per year in 2016, with slightly more autologous (53.5%) than allogeneic HSCT. This represents an increase of >7% per year.

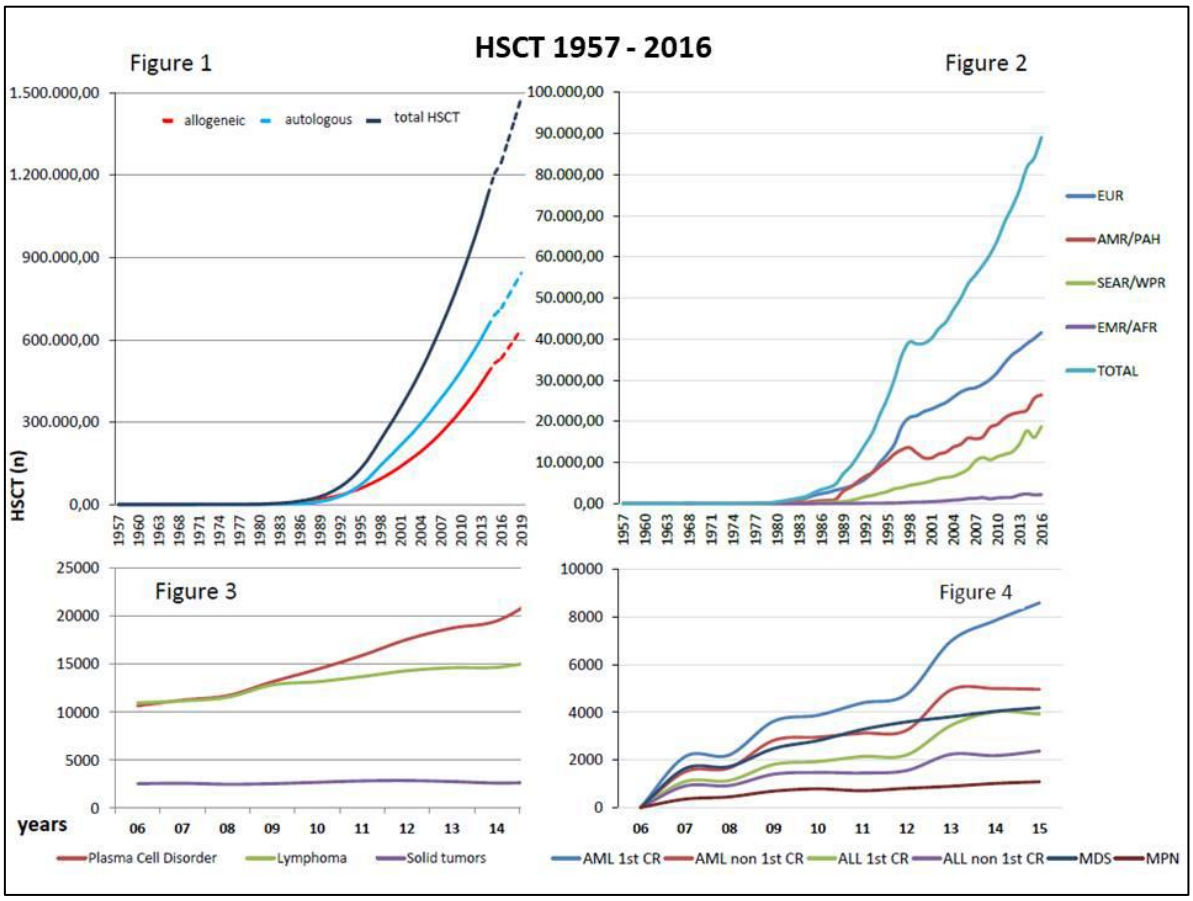


Figure 1 Incidence of HSCT from 1957-2016

1) *grouped by type of HSCT. 2) grouped by continental regions. 3) and 4) grouped by underlying disease. – HSCT incidence. HSCT – hematopoietic stem cell transplant; EUR – Europe; AMR/PAH – Region of the Americas; SEAR/WPR – South-East Asia/ Western Pacific Region; EMR/AFR – Eastern Mediterranean/African Region; AML – Acute myeloid leukemia; CR – complete remission; ALL – Acute lymphoblastic leukemia; MDS – Myelodysplastic syndrome; MPN – myeloproliferative neoplasm. Adapted from Niederwieser et al [(15)].*

Prognostic Impact

Patients with leukemias harboring adverse genetic events are at high risk of relapse after intensive chemotherapy, and post-remission allografting is the only available treatment modality that can result in cure or long-term survival [(14)]. The steep dose-response curve for high-dose melphalan in patients with Myeloma results in meaningful clinical benefits after HSCT and this treatment modality delays progression and improves median overall survival by approximately 12 months [(16)].

In relapsed / refractory diffuse large B cell lymphoma, the most common NHL, the role of HSCT has been prospectively established, and compared to chemotherapy alone, 5-year event-free survival and overall survival were significantly superior in the transplant arm (46% and 53% vs. 12 and 32%, respectively) [17]. In HL, a disease of young adults, autologous HSCT is the standard of care in the relapsed or refractory setting and results in a cure rate of 50% [18].

Disease relapse is the major cause of treatment failure in the first 2–5 years after HSCT. Patients that endure the early post-transplant period can nowadays enjoy relatively long-term survival. In the last few years, studies have presented long-term survival in both types of transplants. In autologous HSCT Vanderwalde et al. (2013) [19] showed a 5-year survival of 75% for 2-year survivors, 81% for 5-year survivors, and 88% for 10-year survivors, and Mahjail et al. (2009) [20] showed a 10-year survival of 52–85% (depending on lymphoma type) for 2-year survivors. In allogeneic HSCT Atsuta et al. (2016) [21] showed a 15-year survival rate of 83% for 2-year survivors; Wingard et al. (2011) [22] showed a 10-year survival rate of 80–92% (depending on disease) for 2-year survivors.

Considering a projection made in 2013, it is presumed that by 2030 there will be more than 500,000 HSCT survivors [23].

1.2 Acute Kidney Injury

Historical background

The analysis of human urine began 6,000 years ago with Babylonian and Egyptian physicians, and it was considered a primary diagnostic tool until the Victorian era. [24]. It was not until 1802 that William Heberden described the clinical course of AKI for the first time in his “Commentaries on History and Cure of Diseases” and named it ischuria renalis. Although Bowman, Charcot, and William Osler made important contributions to the following initial descriptions, AKI only started to be considered a clinical entity when Bywaters and Beal described anuric AKI after crush syndrome during the German bombing of London during World War II (1940–1941) [25]. In 1951, Homer W. Smith introduced the term acute renal failure in his seminal text ‘The Kidney: Structure and Function in Health and Disease” and provided clinical advice for the treatment of anuria by maintaining hemodynamic stability and awaiting renal recovery [26]. The term acute kidney failure endured until the twenty-first century with more than 35 different definitions until 2004, when the term acute kidney injury was introduced by the Acute Dialysis Quality Initiative (ADQI) group formed by both nephrologists and intensivists. This change was based on the recognition that even slight changes in serum creatinine were associated with worse outcomes, that “injury” represented pathobiology better than “failure” and that “kidney” is a more understandable word by the general population than “renal”.

Definitions

AKI is a complex syndrome associated with numerous etiologies and pathophysiological mechanisms that lead to a rapid decrease in renal function and have a recently known negative prognostic impact on the patient. In the literature, we identify more than 35 different definitions for AKI, all based on a rapid increase in serum creatinine or a rapid decline in urinary output. Even with the knowledge of several new urinary and blood biomarkers (27), definition and classification continue to focus on serum creatinine and urinary output.

The Risk Injury Failure Loss of kidney function End-stage kidney disease (RIFLE) classification (28) resulted from a consensus made by the ADQI group and was published in 2004. This classification was the first standardized definition of AKI which was crucial for the comparison and generalization of studies 'results. This allowed to confirm the incidence and severity of AKI in various scenarios and establish AKI severity as an outcome predictor (29). The RIFLE classification considers serum creatinine elevation (at least a 50% rise), estimated glomerular filtration rate (eGFR) reduction (at least a 25% reduction), or urinary output reduction (at least < 0.5 ml/kg/h for more than 6 hours). It is organized into three severity classes (risk, Injury, and Failure - and two outcomes - Loss of kidney function and End-stage kidney disease). The criterion leading to the worst classification is used to define the maximum RIFLE. The deterioration of renal function from baseline must occur within 7 days and persist for more than 24 hours. When baseline serum creatinine is unknown, the Modification of Diet in Renal Disease (MDRD) equation should be used to calculate the baseline serum creatinine (30).

The Acute Kidney Injury Network (AKIN) classification (31), published in 2007 by the AKIN working group, results from the consistent findings that smaller increases in serum creatinine than those considered by RIFFLE were also associated with poor outcomes (32) (33). The AKIN classification does not take into consideration baseline serum creatinine nor eGFR, depending on serum creatinine rise within 48 hours (at least >0.3 mg/dl or >50%) or a decrease in urinary output (at least 0.5 mL/kg/h for more than 6 hours). The diagnosis implies adequate volemia and the exclusion of urinary obstruction. It considers three severity stages and does not take into consideration the two outcome RIFLE classes. This classification improved diagnostic sensitivity and specificity but did not show better prognostic prediction (34) (35).

The most recent definition of AKI, Kidney Disease Improving Global Outcomes (KDIGO) classification [(36)], was proposed in 2012 and resulted from the fusion of the former RIFLE classification and the AKIN classification [(37)] as a means to establish

one classification of AKI for clinical practice, research, and public health. The KDIGO work group presented the KDIGO classification, considering both the above-mentioned classifications and providing simplified and integrated criteria for easier clinical activity and investigation applicability. It considers a serum creatinine increase of at least 0.3 mg/dl within 48 hours, an increase more than 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or a urinary output decrease to less than 0.5 ml/kg/h for 6 hours. AKI stratification follows the stages of the AKIN criteria, except for a simplification of stage 3. This classification was also created with the assumption that it offers advantages over the other two systems in identifying patients with AKI and in predicting outcomes. The KDIGO classification system has been recently assessed in several published studies [38] [39].

Table 1 Comparison of RIFLE, AKIN and KDIGO classifications

	Serum creatinine			Urine output
	RIFLE	AKIN	KDIGO	
Definition	SCr increase ≧50% within 7 days	SCr increase ≧50% or ≧0.3 mg/dL within 48 h	SCr increase ≧0.3 mg/dL within 48 h or ≧50% within 7 days	UO < 0.5 mL/kg/h for 6 h
Staging	RIFLE	AKIN	KDIGO	
RIFLE-Risk AKIN stage 1 KDIGO stage 1	SCr increase ≧50% or GFR decrease >25%	SCr increase ≧50% or ≧0.3 mg/dL	SCr increase ≧0.3 mg/dL within 48 h or ≧50% within 7 days	UO < 0.5 mL/kg/h for 6 h
RIFLE-Injury AKIN stage 2 RIFLE stage 2	SCr increase ≧100% or GFR decrease >50%	SCr increase ≧100%	SCr increase ≧100%	UO < 0.5 mL/kg/h for 12 h
RIFLE-Failure AKIN stage 3 KDIGO stage 3	SCr increase ≧200% or GFR decrease >75% or SCr ≧ 4 mg/dL (with an acute rise ≧0.5 mg/dL)	SCr increase ≧200% or SCr ≧ 4 mg/dL (with an acute rise ≧0.5 mg/dL) or need RRT	SCr increase ≧200% or SCr ≧ 4 mg/dL or need RRT	UO < 0.3 mL/kg/h for 24 h or anuria for 12 h
RIFLE-Loss	Need RRT for >4 weeks			
RIFLE-End stage	Need RRT for >3 months			

Abbreviation: RIFLE, risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcome; SCr, serum creatinine; UO, urine output; GFR, glomerular filtration rate; RRT, renal replacement therapy. Adapted from Tsai T-Y et al [40].

The definitions around AKI continue to evolve. There is growing evidence that patients with previous chronic kidney disease have a considerably significant risk of developing AKI in multiple clinical scenarios and that AKI survivors are at increased risk of developing CKD, defined by the persistence of kidney disease for more than 3 months. Also, AKI and CKD share several risk factors, such as advanced age,

diabetes, and hypertension. These findings have led to the supposition that these entities should be seen as a disease continuum instead of separate entities. Given that AKI is defined as an abrupt decrease in kidney function occurring over 7 days or less and CKD as the persistence of kidney disease for a period of greater than 90 days, the ADQI workgroup proposed in 2017 the introduction of the term acute kidney disease, defined as acute or subacute damage and/or loss of kidney function for more than 7 days and less than 90 days after exposure to an AKI initiating event [41].

Table 2 Criteria for defining AKI, AKD, CKD and NKD

	AKI	AKD	CKD	NKD*
Duration	≤7 days	<3 months	>3 months	NA
Functional criteria	Increase in sCr by ≥50% within 7 days or increase in sCr by ≥0.3 mg/dl (26.5 µmol/l) within 2 days or oliguria for ≥6 hours	AKI or GFR <60 ml/min/ 1.73 m^2 or decrease in GFR by ≥35% over baseline or increase in sCr by >50% over baseline	GFR < 60 ml/ min/1.73 m^2	GFR ≥ 60 ml/min/1.73 m^2, stable GFR (no decrease by 35% within 3 months), stable sCr (no increase by 50% within 3 months or increase by 0.3 mg/dl within 2 days), no oliguria for ≥6 hours
AND/OR	OR	OR	OR	AND
Structural criteria	Not defined	Elevated marker of kidney damage (albuminuria, haematuria or pyuria are most common)	Elevated marker of kidney damage (albuminuria is most common)	No marker of kidney damage

Abbreviation: AKI, Acute Kidney Injury; AKD, Acute Kidney Disease; CKD, Chronic Kidney Disease; NKD, No kidney diseases; sCr, serum creatinine; GFR, glomerular filtration rate; NKD implies no functional or structural criteria according to the definitions for AKI, AKD or CKD.*

Epidemiology and risk factors

The reported incidence of AKI varies from 5–15% in hospitalized patients and 50–60% in critically ill patients. These numbers have increased in the last few years. [41][42].

In a 2013 meta-analysis using the KDIGO definition (data from 2004 to 2012) including 154 studies with data of 3,585,911 people, Susantitaphong reported community-acquired AKI in 8.3% of ambulatory patients and in 20.0–31.7% of patients at various levels of in-hospital care. The average pooled mortality rate was 23% but reached 49.4% in those requiring renal replacement therapy [43]. A study

including more than 18 million patients with AKI from 2001 to 2011 reported an almost fivefold increase in incidence [44].

Many factors may be contributing to this evidence: the increased awareness of clinicians towards this entity, the standardization of the definition, and the establishment of known risk factors such as increased age, chronic kidney disease, diabetes, and exposure to nephrotoxins are some of the factors worth mentioning [43] [45].

Several risk factors for AKI have been identified. From environmental and socioeconomic factors more evident in low-income countries, such as water availability, insufficient health care systems, and insufficient control of infectious diseases [46], to patient-related factors that can be considered modifiable (volume depletion, hypotension, anemia, hypoxia, and use of nephrotoxic drugs) or nonmodifiable (chronic kidney disease, heart failure, liver failure, gastrointestinal disease, diabetes, and sepsis).

The most well-established risk factors for AKI are sepsis, severe trauma, hypovolemia, old age, pre-existing chronic kidney disease, acute organ failures, major surgeries (including cardiac surgery), being in the ICU with exposure to nephrotoxic drugs and opportunistic infections, chemotherapy for leukemia or cancer, autoimmune disorders with rapid progressive kidney injury, cholesterol crystal embolism, and urinary tract obstruction [47].

Prognostic impact

Considering short-term outcomes, AKI has been associated with an increased length of hospital stay and in-hospital mortality. Considering long-term outcomes, AKI has been associated with an increased risk of progression to CKD, an increased risk of cardiovascular events, and long-term mortality (45) (48).

All these outcomes reflect an important economic burden considering the cost of hospital stays, cardiovascular morbidity, renal replacement therapy, and so on.

1.3 Acute Kidney Injury in Hematopoietic Stem Cell Transplant

Definition

We consider AKI to be directly associated with HSCT when it occurs in the first 100 days after HSCT. This timeline relates to the fact that the first 100 days are considered the most critical period for all side effects related to the procedure, and it is used to define most HSCT-related complications. By this time, stem cells have already been engrafted, the highest immunosuppressive period is resolving, and the body is functioning in its new normal.

Although several definitions for AKI in HSCT have been used in the last decade, in the last 5 years, the KDIGO classification has been accepted as the most applicable definition in this population.

Risk factors

During this period, there are risk factors for AKI specific to HSCT-related complications and a higher incidence of known risk factors for AKI in the general population. The complexity and overlap of these occurrences suggest that the cause of AKI in HSCT is often multifactorial. Frequency, timing, and risk factors vary according to patient characteristics, hematologic disease, and the type of transplant performed. Also, different parts of the kidney may be affected, resulting in a wide range of renal abnormalities besides AKI, such as hypertension, thrombotic microangiopathy, albuminuria, and glomerulopathies.

Following a traditional pathophysiological organization of AKI in general, the etiology of AKI in HSCT can be divided into:

- prerenal: related to nausea, vomiting, diarrhea from gastrointestinal GVHD, drug-induced nausea or vomiting, heart failure, venous occlusive syndrome (early), hypovolemia or shock, and the most common septic type.

- renal – through glomerular affection such as thrombotic microangiopathy by acute GVHD, calcineurin inhibitors or total body radiation, membranous nephropathy associated with antibodies to protocadherin FAT1 or minimal change disease; interstitial affection by acute interstitial nephritis through medications of infections (BK virus, adenovirus, EBV); tubular affection by sepsis, venous occlusive syndrome (late), acute GVHD, tumor lysis syndrome, radiocontrast agents
- post-renal: blood clots from hemorrhagic cystitis associated with viral infections and retroperitoneal fibrosis associated with radiotherapy.

Factors contributing to the increased risk of developing AKI deserve special attention in this population:

Sepsis-associated AKI

Sepsis is immunologically characterized by the dysregulated activation of the immune system because of the pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) of injured cells and tissues. [49]. Multiple mechanisms can contribute to injury in sepsis-associated AKI, including systemic and renal inflammation, complement activation, RAAS dysregulation, mitochondrial dysfunction, metabolic reprogramming, microcirculatory dysfunction, and macrocirculatory abnormalities [50]. Also, several aggressions to the kidney may occur simultaneously, like exposure to nephrotoxic drugs, hypovolemia, or hyperchloremia.

Sepsis-associated acute kidney injury has a known worse prognosis than either syndrome separately: longer hospital stays, higher morbidity, and higher mortality [51]. The most updated definition of sepsis-associated acute kidney injury was presented in the consensus report of the 28th Acute Disease Quality Initiative workgroup and published in June 2023. It includes the presence of both consensus sepsis criteria (as defined by Sepsis-3 recommendations) and AKI criteria (as defined by Kidney Disease: Improving Global Outcomes recommendations) when AKI occurs within 7 days from the diagnosis of sepsis. [52].

Patients undergoing HSCT are particularly susceptible to sepsis given their immunocompromised state, resulting not only from the induction regimens needed for the success of this procedure but also from the chronic inflammatory state related to the hematologic disease itself.

Nephrotoxic medication and AKI

Many of the available options used in primary prophylaxis for acute GVHD or for opportunistic infections, as well as first-line treatment for most infections occurring during the first 100 days of HSCT, are nephrotoxic. Nephrotoxicity occurs most frequently through direct kidney injury or acute interstitial nephritis as an idiosyncratic allergic response.

Calcineurin inhibitors are included in several protocols concerning primary prophylaxis for acute GVHD in patients undergoing allogeneic HSCT. These agents are associated with AKI within days after exposure by promoting kidney arteriolar vasoconstriction through activation of the renin-angiotensin-aldosterone system and increasing oxidative stress in the kidney's endothelial cells, and this effect is thought to be dose-dependent. They are also less frequently associated with thrombotic microangiopathy [53].

Acyclovir is used for the prevention and treatment of viral infections in patients receiving stem cell transplant. It can cause AKI within the first 48 hours through the formation of crystals in renal tubules and collecting ducts, resulting in obstruction. AKI occurs especially with IV administration in high doses, which makes it rare for it to occur in prophylactic oral doses. [54]

Aminoglycosides are often used for bacterial infections developed in the first month after HSCT. Aminoglycoside-associated AKI complicates 10–25% of therapeutic courses. It is a consequence of renal vasoconstriction, mesangial contraction, and intracellular accumulation of the drug that leads to alterations in cellular permeability in proximal renal tubules, leading to malfunction and obstruction, resulting in tubuloglomerular feedback activation [55]. AKI tends to develop after 7–10 days of

drug exposure, and proximal tubulopathy or Bartter-like syndrome can be observed. Aminoglycosides are prone to cause AKI in patients undergoing HSCT because these patients often develop conditions favorable to aminoglycoside-associated AKI, such as volume depletion or liver disease, and undergo prolonged exposure and multiple daily doses [56].

Low-dose cotrimoxazole is used as prophylaxis for opportunistic infections in patients undergoing HSCT. Sulfonamide-associated AKI is thought to complicate 11.2% of therapeutic courses and generally occurs within 7 days of treatment. It has been associated with crystalluria, crystal nephropathy, and acute interstitial nephritis. The risk of AKI is higher when sulfonamides are used in high doses, in situations of volume depletion, hypoalbuminemia, and in the presence of acidic urine, considering the acidic nature of sulfamethoxazole and its insolubility at pH < 5.5 [57].

Amphotericin is used to treat invasive, life-threatening fungal infections in patients undergoing HSCT. Although liposomal amphotericin is less nephrotoxic, both liposomal amphotericin and amphotericin B deoxycholate may cause AKI in patients who have other risk factors for AKI [58]. They promote vasoconstriction of the renal vasculature, resulting in hypoperfusion and renal tubular epithelial damage with disruption of cell membranes. They can also be related to urinary potassium wasting and hypokalemia, urinary magnesium wasting and hypomagnesemia, metabolic acidosis due to type 1 renal tubular acidosis, and polyuria due to arginine vasopressin resistance [59].

Graft versus host disease and AKI

GVHD develops when donor T cells respond to recipient tissue antigens secondary to mismatches between the donor and recipient. AKI in acute GVHD has been traditionally associated with dehydration secondary to diarrhea in more severe stages of GVHD but recent studies have suggested that the kidney may be a direct target of acute GVHD [60]. It is now accepted that GVHD is also directly associated with thrombotic microangiopathy, causing AKI. Damage to the kidneys results from

excessive release of tumor necrosis factor-a, interleukin-6, and transforming growth factor-b [61].

Acute thrombotic microangiopathy and AKI

Acute thrombotic microangiopathy in patients undergoing HSCT has specific triggers compared to other patients. It can be caused by medication (mostly related to calcineurin inhibitors used for the primary prophylaxis of acute GVHD), by the GVHD itself, by total body irradiation, or by infections. [62] [63]. Recently, it has also been proposed that HSCT unmasks undiagnosed alternative complement pathway mutations. Clinical presentation characterized by thrombocytopenia, microangiopathic hemolytic anemia, and organ injury including AKI, as well as pathologic findings including endothelial swelling and mesangiolysis in active lesions, fibrin thrombi within capillary loops and arterioles, and double contours of the basement membrane in chronic lesions, are indistinguishable from other scenarios of acute thrombotic microangiopathy [64]. The 2007 International Guidelines from the European Group for Blood and Marrow Transplantation concerning microangiopathy related to HSCT [65] require fulfillment of all of the following criteria: >4% schistocytes in blood; de novo, prolonged or progressive thrombocytopenia (platelet count <50 x 10^9/L or 50% or greater reduction from previous counts); sudden and persistent increase in lactate dehydrogenase concentration; decrease in hemoglobin concentration or increased transfusion requirement; and decrease in serum haptoglobin.

Tumor Lysis Syndrome and AKI

Tumor lysis syndrome is a group of metabolic disorders resulting from the lysis of malignant cells or from high cell turnover and tumor proliferation rates. It is characterized by hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and high levels of blood urea nitrogen. AKI results from cytokine-related kidney damage, crystalline-induced tubular injury (hyperuricemia/hyperphosphatemia), or crystal-independent uric acid-related nephrotoxicity. This is a rare complication after

HSCT, as the hematologic malignancy is often eliminated by the time of the procedure. [66]

Hepatic Sinusoidal Obstruction Syndrome and AKI

Hepatic sinusoidal obstruction syndrome, or veno-occlusive disease, occurs within 30 days of HSCT; it is potentially life-threatening and is associated with AKI [67]. It can occur in up to 13.7% of patients undergoing allogeneic HSCT and 2% of patients undergoing autologous HSCT and appears to be a variant of hepatorenal syndrome. It involves an initial toxic injury to the sinusoidal endothelium that damages endothelial cells, resulting in defenestration in the sinusoidal barrier, and portal hypertension resulting from hepatic sinusoidal injury may lead to decreased renal perfusion and tubular injury [68]. Risk factors include previous liver disease and the use of agents that are toxic to the sinusoidal endothelial cells, like busulfan, cyclophosphamide, and/or total body irradiation [69].

Engraftment Syndrome, Capillary leak syndrome and AKI

Capillary leak syndrome is part of the cytokine release syndrome and presents within two weeks after HSCT. Engraftment syndrome occurs mainly during neutrophil regeneration and is often accompanied by fever and rash with multiorgan dysfunction. These complications of HSCT can cause AKI in the early post-transplant period through the release of proinflammatory cytokines, originating a prerenal injury secondary to intravascular volume depletion and causing direct renal injury by promoting inflammation in the kidney [70].

Marrow Infusion Syndrome and AKI

Cryoprotectants and other technical specificities of the process of stem cell preservation can be responsible for erythrocyte lysis, which, when infused, may cause fever, vomiting, hypotension, abdominal pain, and hemoglobin pigment nephropathy within 24–48 hours of transplantation. Marrow infusion syndrome-associated AKI occurs in less than 2% of patients undergoing HSCT and results

from kidney vasoconstriction, direct hemoglobin cytotoxicity, and intratubular hemoglobin cast formation [71].

BK virus, adenovirus and AKI

BK virus and adenovirus infections have a considerably higher incidence in patients undergoing HSCT, as they can both reactivate after the procedure. They can cause hemorrhagic cystitis that can manifest with massive hematuria, complicating obstruction of the urinary tract or interstitial nephritis [72] [73].

Epidemiology and prognostic impact

Clajus et al. (2012) published one of the first reviews on renal comorbidity after transplantation and the AKI incidence in different modalities of HSCT, considering the studies made until 2012 ranged from 20% to 92% [74]. At that time, the wide range of AKI incidence reported in these studies is explained by the heterogeneity of AKI definitions amongst the studies and the inclusion of different baseline hematologic diagnoses and types of transplants.

In 2020, Kanduri et al. [75] published a meta-analysis including 36 cohort studies with a total of 5144 patients undergoing HSCT, showing a pooled estimated incidence of AKI and severe AKI of 55.1% and 8.3%, respectively. The pooled estimated incidence of AKI using the three AKI definitions—RIFLE, AKIN and KDIGO—was 49.8%. The pooled odds ratios of 3-month mortality and 3-year mortality among patients undergoing HCT with AKI were 3.05 and 2.23, respectively.

In the last four years, studies using KDIGO classification have prevailed, but all the published studies consider only serum creatinine criteria, and the majority tends to include several hematologic diagnoses in the same analysis but tend to divide according to the type of HSCT.

In studies on allogeneic HSCT including several hematologic diagnoses, Gutierrez-Garcia et al. (2020) (76), and the presence of severe AKI had an impact on overall survival; Andronesi et al. (2022) [77] referred to a 68.9% AKI incidence without impact on overall survival; and Madsen et al. (2022) [78] described an AKI incidence of

64.2% with a significant impact on overall survival and on relapse-free survival (although there was no difference in the 2-year incidence of relapse). In studies on autologous HSCT, Andronesi et al. (2019) reported an AKI incidence (KDIGO classification through creatinine criteria and only the first 30 days after HSCT) of 10.4% [79] and did not find higher mortality rates related to AKI.

Chapter 2 - Objectives

With the main objective of performing an epidemiologic evaluation of acute kidney injury in patients with oncological malignancies undergoing HSCT, we present the following questions and specific objectives:

What is the incidence, presentation criteria, and severity of AKI in patients undergoing HSCT considering different hematologic malignancies?

1. To evaluate the cumulative incidence, earlier diagnosis criteria, and severity of AKI according to the KDIGO classification using both creatinine and urinary output criteria in the first 100 days after HSCT
    a. In patients with multiple myeloma undergoing autologous HSCT;
    b. In patients with lymphoma undergoing autologous HSCT;
    c. In patients with leukemia undergoing allogeneic HSCT;

What are the risk factors for AKI in patients undergoing HSCT considering different hematologic malignancies?

2. To define risk factors for AKI according to the KDIGO classification in the first 100 days after HSCT in this population.
    a. In patients with multiple myeloma undergoing autologous HSCT;
    b. In patients with lymphoma undergoing autologous HSCT;
    c. In patients with leukemia undergoing allogeneic HSCT;

What is the prognostic impact of developing AKI during the first 100 days after HSCT in patients undergoing HSCT, considering different hematologic malignancies?

3. To study the association of AKI in the first 100 days after HSCT with relapse-free survival, overall survival and progression to chronic kidney disease.
    a. In patients with multiple myeloma undergoing autologous HSCT
    b. In patients with lymphoma undergoing autologous HSCT
    c. In patients with leukemia undergoing allogeneic HSCT

Is it possible to predict the risk of AKI in patients undergoing HSCT?

4. To calculate a predictive risk score for AKI considering variables available before the HSCT.

Chapter 3 - Materials and Methods

3.1 Chronogram

First year: (2019/2020)	- Meetings with the Department of Hematology and Bone Marrow Transplantation in order to present the project; - Ethics Committee approval; - Start data collection; - Start the program - Portugal Clinical Scholars Research Training (PTCSRT) 2020-2022; - Bibliographic revision;
Second year (2020/2021)	- Continue data collection; - Data analysis of the first subgroup; - Presentation of the first results in an international conference; - Continuation of the program- Portugal Clinical Scholars Research Training (PTCSRT) 2020-2022 - Bibliographic revision;
Third year (2021/2022)	- Conclusion of data collection; - Data analysis of the remaining subgroups; - Presentation of the results in international conferences; - Writing and submission of the first manuscript; - Writing of the second manuscript; - Conclusion of the program -Portugal Clinical Scholars Research Training (PTCSRT) 2020-2022; - Bibliographic revision;
Fourth year (2022/2023)	- Data analysis of the population for predictive risk score; - Presentation of the results in international conferences; - Writing and submission of the third and fourth manuscripts; - Thesis writing;

3.2 Study design and population

We designed a single-center retrospective cohort study.

Our study population included patients who were diagnosed with lymphoma, leukemia, or multiple myeloma and performed HSCT at the CHULN, EPE, between January 2005 and December 2015. CHULN, EPE, includes two tertiary hospitals (Hospital de Santa Maria and Hospital de Pulido Valente), and its geographic assistance area for healthcare services includes around 3.000,000 inhabitants in Portugal. Amongst its various clinical departments, CHULN, EPE has a Department of Hematology and Bone Marrow Transplantation and a Department of Nephrology and Renal Transplantation.

As exclusion criteria, we defined: 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 those with previous HSCT.

In order to answer the first three questions of this dissertation (Chapter 2. Objectives), we analyzed our population separately according to the hematologic malignancy diagnosis and type of HSCT (patients with multiple myeloma undergoing autologous HSCT, patients with lymphoma undergoing autologous HSCT, and patients with leukemia undergoing allogeneic HSCT). For the fourth and last question, we analyzed all the patients included in this study.

3.3 Data Collection

Our data collection was made between February 2020 and November 2022 and included access to the files concerning hospital stays for the HSCT procedure, access to hospital digital databases, including medical appointments, and diagnostic exams performed before and after the hospital stay for each patient.

The file concerning the hospital stay for the HSCT procedure included daily medical records, six-hour period nurses´ records (including urinary output, blood pressure,

heart rate, body temperature, and clinical occurrences during shifts), diagnostic exams (daily blood analysis), and imaging exams.

We collected variables related to:

a) patient demographic characteristics (age, gender, race, body weight, and height), related to patient comorbidities (diabetes mellitus, hypertension, arrythmia, valvular heart disease, ischemic heart disease, cerebrovascular disease, chronic liver disease, intestinal inflammatory disease, peptic ulcer, connective tissue disease, chronic obstructive pulmonary disease, solid-organ cancer, psychiatric disease);
b) oncologic malignancy (the group of oncologic malignancy, stage at diagnosis, specific features for each group) and previous treatment approach (number of previous lines of therapy, number of chemotherapy cycles, exposure to radiotherapy in the past);
c) HSCT (conditioning regimen, graft source, time to engraftment, length of hospital stays, blood results on the first hospital admission day for HSCT, sinusoidal obstructive syndrome, thrombotic microangiopathy, tumor lysis syndrome, sepsis, nephrotoxic drugs, shock, cytomegalovirus infection, AKI (time to AKI), diagnosis criteria, stage of diagnosis, worst stage during hospital stay, AKI stage);
d) follow-up (time to relapse, time to all-cause mortality, and estimated glomerular filtration rate 1 year after HSCT and 3 or 5 years after HSCT);

Patients with lymphoma were followed until death or censored at 36 months (3 years) after HSCT, patients with leukemia and Multiple Myeloma were followed until death or censored at 60 months (5 years) after HSCT. This timeline was defined because patients are often transferred to other hospitals closer to their residence for continued follow-up after these periods.

3.4 Definitions

The conditioning regimens used followed institutional protocols and are mentioned in the results section on each demographic and transplant-related variable table.

Total body irradiation is not available in CHULN EPE, and it is not contemplated in any of our institutional protocols.

We considered serum creatinine at the last medical appointment before hospital admission for HSCT to be baseline serum creatinine. Baseline glomerular filtration rate was estimated according to the CKD-EPI equation [80], using baseline serum creatinine.

AKI diagnosis was made based on daily values of serum creatinine and 6-hour urinary output since the time of hospital admission for HSCT until hospital discharge, as well as all other hospital admissions or weekly evaluations in the outpatient clinic in the first 100 days after HSCT. AKI was defined by KDIGO criteria [81] (any of the following: increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urinary output <0.5 ml/kg/h for 6 hours). Stage of AKI followed the KDIGO classification, considering the worst serum creatinine value and/or longest period of urinary volume reduction during hospital stay for HSCT. Moderate to severe AKI was defined as AKI stage 2 and AKI stage 3.

Chronic Kidney Disease (CKD) was defined as a persistent decrease in estimated glomerular filtration rate to below 60 mL/min/1.73 m2, according to the definition of KDIGO [82].

The Hematopoietic cell transplantation – specific comorbidity index (HCT-CI) [83] was calculated according to the latest validated version, considering patients comorbidities.

Sepsis was considered when patients presented with a temperature ≥38°C or <36°C, a white blood cell count >10 000/mm3 or <4000/mm3, and a positive blood culture for bacteria [84].

Shock was considered when patients presented with a cardiac frequency > 90 bpm, systolic blood pressure < 90 mmHg, and at least one lactate determination > 2 mmol/L or 22 mg/dL.

Oral mucositis was graded according to the World Health Organization's (WHO's) Oral Toxicity Scale [85].

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

The diagnosis of multiple myeloma was made according to the International Multiple Myeloma Working Group (IMWG) Criteria [86]. Multiple myeloma staging was made using the International Staging System for Myeloma (ISS) [87]. The associated AL amyloidosis was diagnosed by demonstration of Congo red staining (kidney or subcutaneous fat biopsy).

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 by morphological analysis.

Overall survival was calculated in days from HSCT until any cause of death.

3.5 Statistical analysis

We describe categorical variables as the total number and respective frequencies, continuous variables with a normal distribution as the mean ± standard deviation, and variables not following a normal distribution as median and interquartile range.

We followed the European Group for Blood and Marrow Transplantation guidelines on statistical methodology published in 2013 [88].

We approached AKI as a time-dependent variable, considering the first 100 days after HSCT. In order to calculate the cumulative incidence of AKI and to analyze factors predicting AKI, we used the Fine and Gray method [89], a survival analysis method considering competing events, and death was considered a competing event. For factors predicting AKI, we first performed univariable analysis and then used backward stepwise regression to create the final multivariable model

To evaluate the impact of AKI on disease-free survival during the follow-up, we used the Fine and Gray method, considering death as a competing event. We performed univariable analysis for the variable time until relapse and then used backward stepwise regression to create the final multivariable model.

To analyze the impact of AKI on overall survival, we used additive Cox proportional hazards regression models to analyze time until death from all causes. The Cox proportional hazards assumption was checked using formal statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. We performed univariable analysis for the variable time until death and then used backward stepwise regression to create the final multivariable model.

The incidence of CKD and eGFR reduction >25% was calculated at the end of the first year and at the end of the follow-up period, and the association with AKI was evaluated.

To create the predictive risk score for AKI considering variables available before the HSCT, we used the Fine and Gray method, considering death as a competing event, to perform univariable and multivariable analyses of factors predicting AKI available before the HSCT. To establish the multivariable model for the creation of the clinical score, continuous variables that presented a $p<0.200$ were dichotomized according to the Liu index [90]. The resulting categorical variables were tested for their association with the risk of incident AKI, and a multivariable model was created through a backward stepwise regression (entry criteria: $p<0.20$). Harrel's C-Statistic was used to evaluate the performance of the model, and a risk score was created by attributing points corresponding to the nearest integer of 2 times each covariate's Hazard Ratio. The Liu index was used further to establish the optimal cut-off for the clinical risk score. A log-rank test and respective reverse Kaplan-Meier curves were used to compare the event distributions of the resulting score categorical variable.

Crude and adjusted hazard ratios were estimated with corresponding 95% confidence intervals (CIs). A level of significance of $\alpha = 0.05$ was considered.

Missing data for all variables represented less than 10%, therefore no imputation

techniques were used.

For data analysis, we used the statistical software package STATA for Windows (StataCorp). 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/.)

3.6 Ethics committee

This study was approved by the local Ethics Committee – Comissão de Ética do Centro Académico de Medicina de Lisboa on the 13th of October of 2020 (reference number 334/20) in agreement with institutional guidelines. Informed consent was waived by the Ethical Committee due to the retrospective and non-interventional nature of the study.

Chapter 4 - Results

4.1 AKI in patients with Multiple Myeloma undergoing autologous HSCT

Population description

One hundred and eighty-two patients with multiple myeloma underwent autologous HSCT during the referred period. Thirty-nine patients presented at least one exclusion criteria. One hundred and forty-three patients were included in our final analysis. Table 3 shows demographic variables, Multiple Myeloma-related variables and transplant-related variables.

Table 3 Patients' baseline characteristics, Multiple Myeloma characterization and transplant related variables

Patient´s Characteristics and comorbidities	Category	n (%)	P50 (P25 - P75)
Age at transplant (years)			59.2 (50.5 - 63.6)
Gender	Female	55 (38.5)	
	Male	88 (61.5)	
Race	caucasian	130 (90.9)	
	non caucasian	13 (9.1)	
BMI (Kg/m2)			26.1 (23.4 - 29.4)
HCT-CI	0-1	120 (83.9)	
	≥2	23 (16.1)	
Diabetes Mellitus		18 (12.6)	
Hypertension		53 (37.1)	
Cardiac Heart Failure		10 (7)	
baseline eGFR (ml/min/1.73m2)			100.4 (89.5 - 110.8)
Chronic Kidney Disease	eGFR < 60 ml/min/1.73m2	15 (10.5))	
Multiple Myeloma characteristics and previous treatment			
Multiple Myeloma	IgG	90 (62.9)	
	IgA	21 (14.7)	
	IgD	3 (2.1)	
	Free Light Chain Kappa	17 (11.9)	
	Free Light Chain Lambda	12 (8.4)	
Light chain domain	Kappa	87	
	Lambda	51	
Multiple Myeloma and Amyloidosis		5 (3.5)	
ISS	Stage I	70 (49.0)	
	Stage II	38 (26.6)	
	Stage III	35 (24.5)	
Cytogenetic abnormalities		49 (34.3)	
Bone Marrow plasma cells			30 (17 - 67)
M-protein level (gr/dl)			3.3 (2.2 - 6.6)
Serum B2-microglobulin			3.1 (1.7 - 5.5)
Serum Ig (mg/dl)			5880 (3490 - 9200)
Light chain (mg/dl)			3560 (890 - 7800)
Serum K/L			4.52 (0.26 - 56.35)
Nr of previous lines of therapy			1 (1 - 2)
Nr of chemotherapy cycles			4 (3 -4)
Radiotherapy in the past		49 (34.5)	
Auto-HSCT characteristics and complications			
Graft source	Peripheral blood	136 (95.1)	
	Bone Marrow	7 (4.9)	
Melphalan	1 day	15 (10.6)	
	2 days	126 (89.4)	
Period of aplasia (days)			11 (11 - 12)
Sepsis		38 (26.6)	
Fever		111 (77.6)	
Nephrotoxic drugs		106 (74.1)	
Mucositis	Grade 1-4	80 (55.9)	
	Grade 3-4	16 (11.2)	
TMA/ TLS/ VOD		3 (2.1)	
Shock		4 (2.8)	
At hospital admission day:			
Hemoglobin (gr/dl)			11.7 (10.8 - 12.4)
Leukocytes (cells/mm3)			5450 (4120 - 6610)
Neutrophils (cells/mm3)			3375 (2330 - 4765)
Lymphocytes (cells/mm3)			1066 (760 - 1500)
Platelets (/µl)			198000 (151000 - 270000)
Urea (mg/dl)			33 (28 - 44)
Uric Acid (mg/dl)			5 (4.1 - 6.0)
Calcium (mg/dl)			9.1 (8.7 - 9.4)
Phosphate (mg/dl)			3.4 (3.0 - 2.9)
Reactive C Protein (mg/dl)			0.25 (0.09 - 0.67)
Lactate Dehydrogenase (U/L)			333 (297 - 390)
Albumin (g/dL)			3.9 (3.7 - 4.2)
Alanine Transaminase (U/L)			18 (14 - 27)
Total Bilirubin (mg/dl)			0.5 (0.4 - 0.5)
Serum B2-microglobulin /mg/L)			2.4 (1.6 - 3.1)

Legend table 3: P50 – median; P25 – 25th percentile; P75 – 75th percentile; BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; Nr – number; eGFR – estimated glomerular filtration rate; Ig – immunoglobulin; ISS – International Staging System; TMA/TLS/VOD - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease.

Cumulative incidence, earlier diagnosis criteria and severity of AKI

The AKI cumulative incidence in the first 100 days after HSCT was 49.7% and AKI occurred at a median time of 8 (5-13) days after HSCT. Figure 2. Moderate-to-severe AKI cumulative incidence was 14.1%.

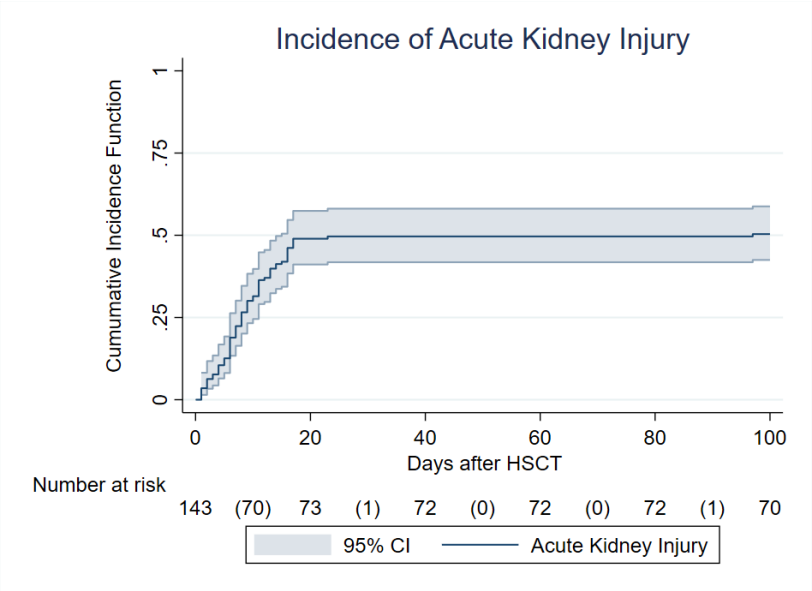


Figure 2 AKI cumulative incidence in patients with Multiple Myeloma undergoing autologous HSCT.

Considering patients with AKI, the earlier diagnosis criteria for AKI were: serum creatinine elevation in 71.8%; urinary output reduction in 18.3% and both serum creatinine elevation and urinary output reduction in 9.9%.

On the first day of AKI, the severity of AKI was stage 1 in 85.9%, stage 2 in 5.6%, and stage 3 in 8.5% of cases. The highest severity stage registered was stage 1 in 71.8%, stage 2 in 15.5% and stage 3 in 12.7%.

Risk factors for AKI

In the univariable analysis considering death as a competing risk (Table 4) variables associated with AKI were BMI (HR:1.04, 95%CI:1.01-1.11; p=0.048), HCT-CI score ≥2 (HR:2.06, 95%CI:1.24-3.43; p=0.005), baseline eGFR (HR:0.98, 95%CI:0.97-0.99; p<0.001), CKD (HR:3.3, 95%CI:1.62-6.71; p=0.001), International Staging System (ISS) grade (HR:1.55, 95%CI:1.18-2.04; p=0.002), fever (HR:2.01, 95%CI:1.02-3.97; p=0.044), sepsis (HR:1.78, 95%CI:1.11-2.85; p=0.016), nephrotoxic drugs (HR:2.56, 95%CI:1.30-5.06; p=0.007), Mucositis (HR:1.91, 95%CI:1.16-3.14; p=0.001), Mucositis grade 3 and 4 (HR:2.94, 95%CI:1.75-4.92; p<0.001).

Table 4. Univariable analysis for AKI in patients with Multiple Myeloma undergoing autologous HSCT.

Patient´s Characteristics and comorbidities	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Age at transplant (years)	1.02	1.00	1.05	0.057
Gender (reference Female)	1.24	0.77	1.99	0.379
Race (reference non caucasian)	1.18	0.54	2.57	0.684
BMI (Kg/m2)	1.04	1.00	1.10	0.048
HCT-CI (reference <2)	2.06	1.24	3.43	0.005
Diabetes Mellitus	1.57	0.88	2.79	0.120
Hypertension	1.19	0.75	1.90	0.462
Cardiac Heart Failure	1.63	0.80	3.31	0.175
baseline eGFR (ml/min/1.73m2)	0.98	0.97	0.99	<0.001
Chronic Kidney Disease	3.3	1.62	6.71	0.001
Multiple Myeloma characteristics and previous treatment				
Light Chain domain (reference lambda)	1.18	0.72	1.92	0.508
Multiple Myeloma and Amyloidosis	2.12	0.92	4.94	0.078
ISS	1.55	1.18	2.04	0.002
Cytogenetic abnormalities	1.56	0.99	2.46	0.055
Bone Marrow plasma cells	1.00	0.99	1.01	0.96
M-protein level (gr/dl)	0.99	0.94	1.03	0.609
Serum B2-microglobulin	1.04	1.00	1.08	0.114
Nr of previous lines of therapy	1.25	0.82	1.92	0.288
Nr of chemotherapy cycles	0.92	0.77	1.1	0.375
Radiotherapy in the past	1.18	0.74	1.87	0.484
HSCT characteristics and complications				
Graft source	1.24	0.40	3.88	0.711
Melphalan (reference 1 day)	1.26	0.63	2.54	0.513
Period of aplasia (days)	1.03	0.95	1.1	0.500
Sepsis	1.78	1.11	2.85	0.016
Fever	2.01	1.02	3.97	0.044
Nephrotoxic drugs	2.56	1.30	5.06	0.007
Mucositis 1-4	1.91	1.16	3.14	0.010
Mucositis 3-4	2.94	1.75	4.92	<0.001
TMA/ TLS/ VOD	0.69	0.73	6.43	0.741
Shock	2.61	0.69	9.85	0.157
At hospital admission day:				
Hemoglobin (gr/dl)	0.9	0.76	1.06	0.219
Leukocytes (cells/mm3)*	1.02	0.99	1.03	0.157
Neutrophils (cells/mm3)*	1.02	1.00	1.03	0.021
Lymphocytes (cells/mm3)	0.99	0.99	1.00	0.302
Platelets (/µl)	0.99	0.99	1.00	0.426
Urea (mg/dl)	1.03	1.02	1.04	<0.001
Uric Acid (mg/dl)	1.01	0.97	1.05	0.759
Calcium (mg/dl)	0.74	0.49	1.10	0.141
Phosphate (mg/dl)	0.68	0.47	0.99	0.049
Reactive C Protein (mg/dl)	0.99	0.93	1.06	0.824
Lactate Dehydrogenase (U/L)**	1.06	1.02	1.10	0.002
Albumin	1.01	0.94	1.08	0.874
Alanine Transaminase (U/L)	0.98	0.96	1.00	0.077
Total Bilirubin (mg/dl)	0.65	0.25	1.69	0.380
Serum B2-microglobulin	1.04	0.99	1.08	0.114

Legend table 4. BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; eGFR – estimated glomerular filtration rate; ISS – International Staging System; Nr – number; TMA/TLS/VOD - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease.

Variables independently associated with a higher incidence of AKI are shown in Table 5 and include BMI (HR:1.08, 95%CI:1.02-1.13; p=0.004), HCT-CI score ≥2 (HR:1.85, 95%CI:1.08-3.17; p=0.025), CKD (HR:2.06, 95%CI:1.05-4.04; p=0.035), Multiple Myeloma and Amyloidosis (HR:2.25, 95%CI:1.25-4.06; p=0.007), Mucositis grade 3 and 4 (HR:2.19, 95%CI:1.25-3.86; p=0.006), and nephrotoxic drugs (HR:2.0856, 95%CI:1.04-4.19; p=0.039).

Table 5 Multivariable analysis for AKI in patients with Multiple Myeloma undergoing autologous HSCT.

Patient´s and transplant related variables	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
BMI (Kg/m2)	1.08	1.02	1.13	0.004
HCT-CI ≥2	1.85	1.08	3.17	0.025
Chronic Kidney Disease	2.06	1.05	4.04	0.035
Multiple Myeloma and Amyloidosis	2.25	1.25	4.06	0.007
Mucositis Grade 3 and 4	2.19	1.25	3.86	0.006
Nephrotoxic drugs	2.08	1.04	4.19	0.039

BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index.

Impact of AKI on overall survival and relapse-free survival

The median overall survival was 18.7 months. In the first year after HSTC, 14 (9.7%) patients died. At the end of the 5-year follow-up period, 51 (35.7%) patients had died.

In univariable analysis, variables with an impact on lower overall survival were moderate to severe AKI (HR:1.95; 95%CI:1.26-2.98; p=0.040) (Figure 3) ISS (HR:1.69; 95%CI:1.22-2.35; p=0.002), cytogenetic abnormalities (HR:2.21; 95%CI:1.27-3.83;p=0.005) and relapse (HR:1.25 ;95%CI:0.71-2.19;p=0.043).

In our multivariable model, variables with an independent impact on lower overall survival were diabetes mellitus (HR:3.29.76, 95% CI:1.01-9.72), relapse (HR:3.05, 95% CI:1.12-8.31), cytogenetic abnormalities (HR:2.36, 95% CI:1.01-5.53), moderate to severe AKI (HR:1.62, 95% CI:1.15-2.31) and BMI (HR:1.10, 95% CI:1.00-1.21).

Table 6.

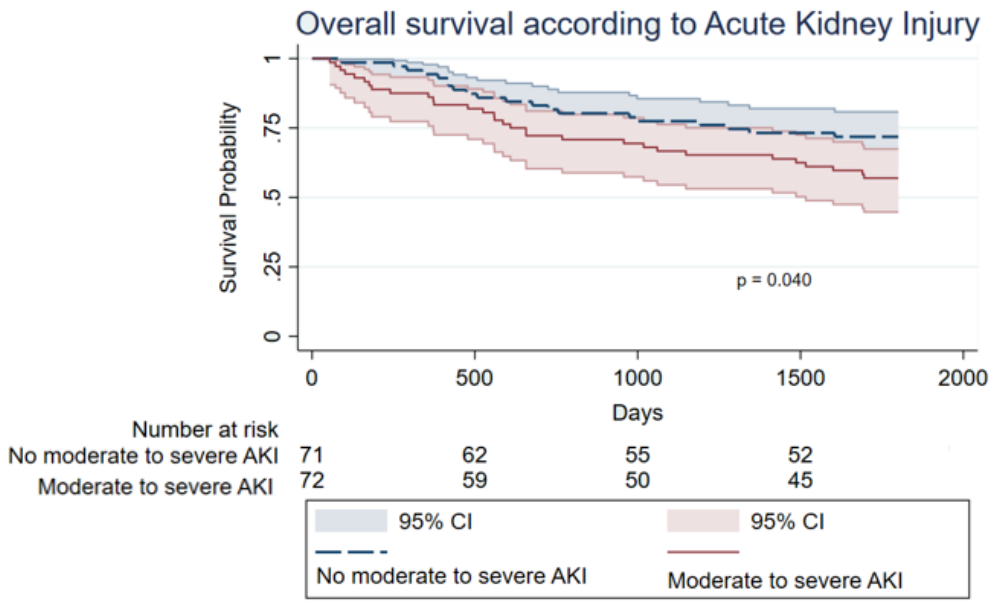


Figure 3 Overall survival and moderate-to-severe AKI in Multiple Myeloma undergoing autologous HSCT

Table 6 Multivariable analysis for mortality in patients with Multiple Myeloma undergoing autologous HSCT

Variables	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Age at transplant (years)	0.98	0.94	1.04	0.711
Gender (reference Female)	0.52	0.20	1.30	0.160
BMI (Kg/m2)	1.10	1.00	1.21	0.045
Diabetes Mellitus	3.29	1.01	9.72	0.048
Hypertension	1.04	0.97	1.02	0.807
Moderate to Severe AKI	1.62	1.15	2.31	0.045
ISS stage	1.67	0.89	3.14	0.113
Cytogenetic abnormalities	2.36	1.01	5.53	0.049
Serum B2-microglobulin at diagnosis	1.02	0.95	1.09	0.564
Relapse	3.05	1.12	8.31	0.029

Legend table 6. BMI - body mass index; AKI – Acute Kidney Injury; ISS – International Staging System.

The cumulative relapse incidence was 61.8% five years after HSCT. The median disease-free overall survival was 43.6 months. No statistically significant association

was found between AKI (nor moderate-to-severe AKI, nor severe AKI) and lower disease-free overall survival.

Impact of AKI on CKD and loss of renal function

The median eGFR prior to HSCT was 100.4 (89.5–110.8) mL/min/1.73 m2 and 10.5% of patients had CKD.

At the end of the first year, the median eGFR was 88.6 (68.6-103.3) mL/min/1.73m2, an eGFR reduction > 25% was observed in 18.4% of the patients, and CKD prevalence was 17.5%. At the end of the five years, the median eGFR was 82.6 (60.5–94.8) mL/min/1.73 m2, an eGFR reduction > 25% was verified in 32.1% of the patients, and CKD prevalence was 27.5%.

No statistically significant association was found between AKI in the first 100 days after HSCT and eGFR reduction > 25% ($p = 0.819$) or CKD prevalence ($p = 0.1011$).

4.2 AKI in patients with Lymphoma undergoing autologous HSCT

Population description

One hundred and forty-three patients with lymphoma were submitted to autologous HSCT at our center between January 2005 and December 2015. Among these patients, 28 were excluded for presenting at least one exclusion criteria, and 115 were eligible for the study. Patients' baseline characteristics and transplant-related aspects are shown in Table 7.

Table 7 Patients' baseline characteristics, Lymphoma characterization and transplant related variables

Patients Characteristics	Category	n (%)	P50 (P25 - P75)
Age at transplant (years)			50.2 (33.9 - 59.5)
Gender	Male	59 (51.3)	
Race	Caucasian	105 (91.3)	
BMI (Kg/m2)			25.3 (21.8 - 35.9)
HCT-CI	0-1	97 (84.4)	
	≥2	18(15.6)	
Hematologic Diagnosis	B-cell lymphomas	73 (63.5)	
	Hodgkin lymphomas	37 (32.2)	
	T-cell lymphomas	5 (4.4)	
Nr of prior cycles of therapy			9 (7 - 10)
Previous radiotherapy	yes	22 (19.3)	
basal eGFR (ml/min/1,73m2)			107.5 (94.3 - 124.6)
Conditioning Regimen	BEAM	109 (94.8)	
	TEAM	6 (5.2)	
Graft source	perihperal blood	111 (96.5)	
	bone marrow	4 (3.5)	
Time to engraftment (days)			10 (10 - 11)
Sepsis		26 (22.6)	
Nephrotoxic drugs		103 (89.6)	
Mucositis		74 (64.4)	
TMA/TLS/VOD		6 (5.3)	
Shock		8 (6.9)	
At hospital admission day:			
Hemoglobin (gr/dl)			11.5 (10.3 - 12.7)
Leukocytes (cells/mm3)			5620 (4000 - 7340)
Neutrophils (cells/mm3)			3530 (2490 - 5290)
Lymphocytes (cells/mm3)			1040 (800 - 1820)
Platelets (/µl)			194000 (140000 - 273000)
Urea (mg/dl)			34 (28 - 39)
Uric Acid (mg/dl)			5.2 (4.2 - 6.0)
Calcium (mg/dl)			9.2 (8.9 - 10.0)
Phosphate (mg/dl)			3.6 (3.2 - 4.1)
Reactive C Protein (mg/dl)			0.52 (0.21 - 1.00)
Lactate Dehydrogenase (U/L)			342 (297 - 419)
Albumin (mg/dl)			4.1 (3.8 - 4.4)
Alanine Transaminase (U/L)			21 (15 - 30)
Total Bilirubin (mg/dl)			0.4 (0.3 0.6)

Legend table 7 - P50 – median; P25 – 25th percentile; P75 – 75th percentile ; BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; Nr – number; eGFR – estimated glomerular filtration rate; BEAM – carmustine, etoposide, cytarabine and melphalan; TEAM - thiotepa, etoposide, cytarabine and melphalan; TMA/TLS/SOS - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease. .

Cumulative incidence, earlier diagnosis criteria and severity of AKI

The AKI cumulative incidence was 63.7% at 100 days after autologous HSCT. (Figure 4) The moderate-to-severe AKI cumulative incidence was 27.1% at 100 days after autologous HSCT.

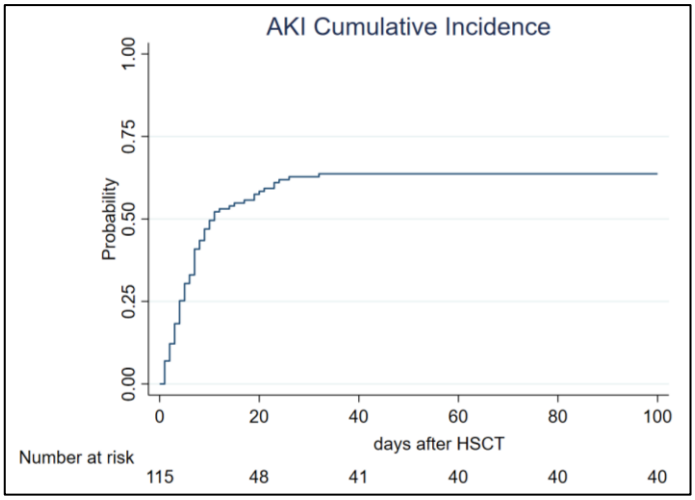


Figure 4 AKI cumulative incidence in patients with Lymphoma undergoing autologous HSCT.

The earlier diagnosis criteria for AKI were a serum creatinine rise alone in 54.8% of patients and a urinary output reduction alone in 41.1% of patients. Both serum creatinine rise and urinary output reduction were observed on the first day of AKI in 4.1% of patients.

On the first day of AKI, patients presented the following severity: AKI stage 1 = 80.8%, AKI stage 2 = 12.3%, and AKI stage 3 = 6.9% (moderate-to-severe AKI in 19.2%). As AKI occurred, the highest severity registered was AKI stage 1 = 57.5%, AKI stage 2 = 17.8%, and AKI stage 3 =24.7% (moderate to severe AKI in 42.5%).

Risk factors for AKI

In the univariable analysis, the predictor variables with impact on AKI were HCT-CI score ≥2 (HR:1.74, 95%CI:1.04-2.90; p=0.034), use of nephrotoxic drugs (HR:3.12, 95%CI:1.18-8.20; p=0.021), mucositis (HR:2.13, 95%CI:1.28-3.52; p=0.003),

thrombotic microangiopathy or sinusoidal obstructive syndrome ((HR:2.52, 95%CI:1.41-4.50; p=0.002), shock (HR:4.11, 95%CI:2.28-7.45;p=<0.001). Table 8

Table 8 Univariable analysis for AKI in patients with Lymphoma undergoing autologous HSCT.

Patients and transplant related Characteristics	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Age at transplant (years)	1.00	0.99	1.02	0.393
Gender	0.84	0.54	1.31	0.457
Race	0.94	0.38	2.35	0.903
BMI (Kg/m2)	1.03	0.99	1.08	0.185
HCT-CI ≥2	1.74	1.04	2.90	0.034
Hematologic Diagnosis:				
Hodgkin lymphomas comparing B-cell lymphomas	1.10	0.67	1.81	0.69
B-cell lymphomas comparing T-cell lymphomas	1.21	0.53	2.80	0.648
Hodgkin lymphomas comparing T-cell lymphomas	1.33	0.56	3.18	0.532
Nr of prior cycles of therapy	0.98	0.91	1.05	0.647
Previous radiotherapy	1.00	0.57	1.77	0.977
basal eGFR (ml/min/1,73m2)	0.99	0.98	1.00	0.192
Conditioning Regimen	0.63	0.22	1.82	0.398
Graft source	1.74	0.55	5.55	0.348
Time do engraftment (days)	0.95	0.82	1.11	0.54
Sepsis	0.80	0.50	1.26	0.347
Nephrotoxic drugs	3.12	1.18	8.20	0.021
Mucositis	2.13	1.28	3.52	0.003
TMA/TLS/VOD	2.52	1.41	4.50	0.002
Shock	4.11	2.28	7.45	<0.001
At hospital admission day:				
Hemoglobin (gr/dl)	1.01	0.87	1.16	0.908
Leukocytes (cells/mm3)	1.00	1.00	1.00	0.447
Neutrophils (cells/mm3)	1.00	0.99	1.00	0.672
Lymphocytes (cells/mm3)	1.00	0.99	1.00	0.523
Platelets (/µl)	1.00	0.99	1.00	0.603
Urea (mg/dl)	1.01	0.99	1.01	0.172
Uric Acid (mg/dl)	1.06	0.94	1.21	0.326
Calcium (mg/dl)	0.88	0.56	1.40	0.586
Phosphate (mg/dl)	0.92	0.70	1.20	0.523
Reactive C Protein (mg/dl)	0.96	0.88	1.04	0.312
Lactate Dehydrogenase (U/L)	1.00	1.00	1.00	0.292
Albumin (mg/dl)	0.94	0.59	1.52	0.812
Alanine Transaminase (U/L)	1.00	0.99	1.01	0.333
Total Bilirubin (mg/dl)	0.92	0.76	1.14	0.481

Legend table 8 - BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; Nr – number; eGFR – estimated glomerular filtration rate; BEAM – carmustine, etoposide, cytarabine and melphalan; TEAM - thiotepa, etoposide, cytarabine and melphalan; TMA/TLS/VOD - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease.

In the multivariable analysis, variables independently associated with a higher incidence of AKI included: nephrotoxic drugs (HR:2.87, 95%CI:1.07-7.65; p=0.035), mucositis (HR:1.95, 95%CI:1.16-3.29; p=0.012) and shock (HR:2.63, 95%CI:1.19-5.85; p=0.017). (Table 9).

Table 9 Multivariable analysis for AKI in patients with Lymphoma undergoing autologous HSCT.

Patients and transplant related Characteristics	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Nephrotoxic drugs	2.87	1.08	7.65	0.035
Mucositis	1.95	1.16	3.29	0.012
MAT/TLS/VOD	2	0.73	5.54	0.182
Shock	2.64	1.19	5.85	0.017
Gender	0.97	0.61	1.52	0.882
BMI	1.02	0.97	1.08	0.428
HCT-CI ≥ 2	1.48	0.81	2.69	0.200
Age at transplant	0.99	0.97	1.01	0.378
basal eGFR	0.99	0.98	1.00	0.125
Graft source	1.71	0.66	4.44	0.273
Conditioning Regimen	0.69	0.22	2.16	0.523

Legend table 9 - BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; eGFR – estimated glomerular filtration rate;; TMA/TLS/VOD - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease.

Impact of AKI on overall survival and relapse-free survival

At the end of the three years after autologous HSCT, 42 (36.5%) patients had died. Fifty two percent of deaths occurred within the first year after autologous HSCT.

In univariable analysis, the variables with impact on mortality were relapse (HR:6.24, 95%CI:2.94-13.24; p=<0.001) and moderate to severe AKI (HR:2.04, 95%CI:1.06-3.94; p=0.033).

In multivariable model, the variables that were independently associated with a lower overall survival were relapse (HR:5.34, 95%CI:2.55-22.30; p=<0.001), BMI (HR:0.91, 95%CI:0.84-0.91; p=0.025) and moderate to severe AKI (HR:2.05, 95%CI:1.10-3.82; p=0.024). (Table 10).

Table 10. Multivariable analysis for mortality in patients with Lymphoma undergoing autologous HSCT.

Patients and transplant related Characteristics	Hazard ratio estimate	Standard error	95% confidence interval		p-value
			lower limit	upper limit	
Relapse	6.24	2.39	2.94	13.23	<0.001
Moderate to severe AKI	2.04	0.68	1.06	3.94	0.033
Age at transplant	1.02	0.01	0.99	1.04	0.18
Race	3.42	3.69	0.41	28.52	0.256
BMI	0.91	0.04	0.84	0.99	0.025
HCT-CI≥ 2	2.08	0.88	0.91	4.76	0.083

Legend table 10 - AKI – Acute Kidney Injury; BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index;

Overall survival according to moderate-to-severe AKI is shown in Figure 5.

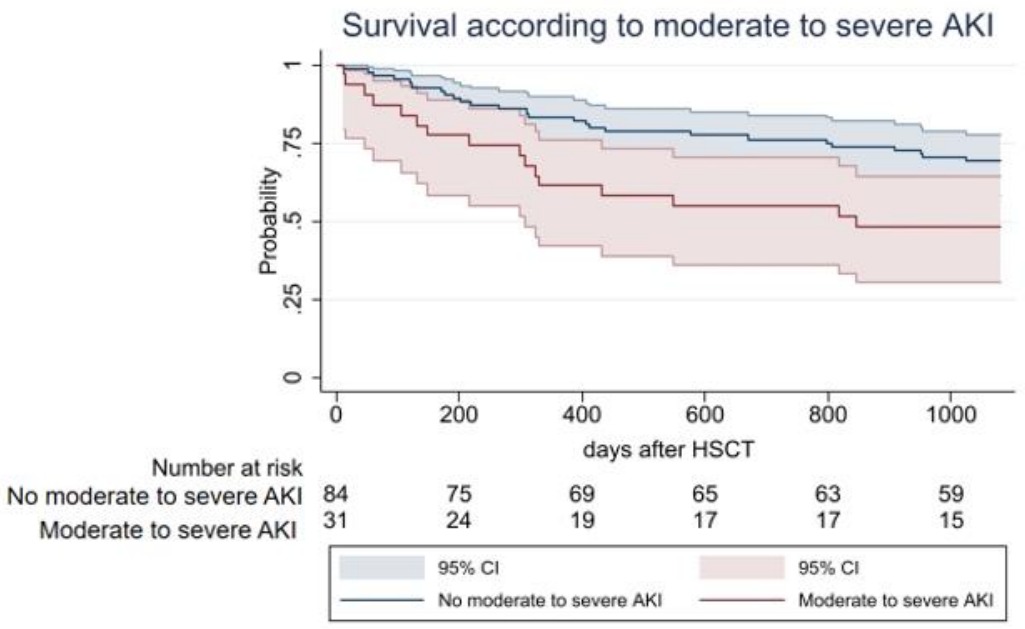


Figure 5 Overall survival and moderate to severe AKI in Lymphoma undergoing autologous HSCT.

AKI – Acute Kidney Injury; CI – confidence interval; HSCT – Hematopoietic Stem Cell Transplant.

Cumulative incidence of relapse was 45.2% at three years after HSCT. No statistically significant association was found between AKI (nor moderate-to-severe AKI) and lower disease-free overall survival.

Impact of AKI on CKD and loss of renal function

None of the patients had CKD previous to HSCT and their median eGFR was 107.5 (94.3-124.6) mL/min/1.73 m2. One year after HSCT none of the survivors had CKD and the median eGFR was 103.7 (87.9-121.6) mL/min/1.73 m. Despite the absence of CKD, 31.2% of the survivors had an eGFR reduction superior to 25% compared to the baseline previous to HSCT. No association was found between this reduction and previous AKI (p=0.730).

Three years after HSCT 2.2% of the survivors had CKD and the median eGFR was 98.6 (80.1 – 115.8) mL/min/1.73 m. An eGFR reduction superior to 25% was registered in 31.8% of the survivors when comparing to the baseline eGFR previous to HSCT and 10% when comparing to eGFR 1 year after HSCT. No association was found between this reduction and previous AKI (p=0.113).

4.3 AKI in patients with Leukemia undergoing allogeneic HSCT

Population description

Between January 2005 and December 2015, 209 patients diagnosed with leukemia were submitted to allo-HSCT in our center. 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 11.

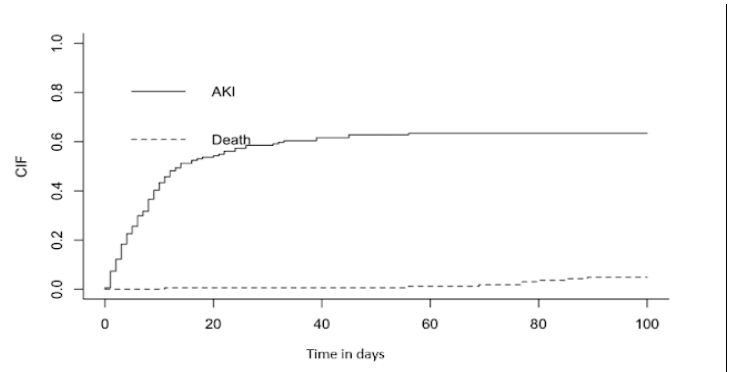
Table 11 Patients' baseline characteristics, Leukemia characterization and transplant related variables

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 lines 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)	
Conditioning Regimen	Non-myeloablative	117(71.3)	
	Myeloablative	47(28.7)	
Donor	Related donor	92(56.1)	
	Unrelated/panel donor	72(43.9)	
Graft source	peripheral blood	142(86.6)	
	bone marrow	22(13.4)	
Time to engraftment (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/ VOD		6(0.04)	
At hospital admission day:			
Hemoglobin (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 (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 11 - 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/ VOD – Thrombotic microangiopathy/Tumor Lysis Syndrome/ Veno-occlusive disease*

Cumulative incidence, earlier diagnosis criteria and severity of AKI

AKI cumulative incidence considering death as a competing event was 58.5% at day 30 and 63.4% at day 100 after HSCT. Figure 6.



Incidence estimates at time points

Time	0	10	20	40	60	80	100
cumulative AKI incidence	0.006098	0.4329	0.542683	0.615854	0.6346	0.63455	0.63455
cumulative death 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 6 AKI cumulative incidence in patients with Leukemia undergoing allogeneic HSCT.

AKI – Acute Kidney Injury; CIF – cumulative incidence function of Acute Kidney Injury; HSCT – Hematopoietic Stem Cell Transplant.

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.

Risk factors for AKI

The univariable analysis considering death as a competing risk is presented in Table 12. In this analysis variables associated with AKI incidence were: HCT-CI ≥2 (HR:1.58 ;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) and shock (HR:2.07;95%CI:1.41-3.02;p<0.001).

Table 12. Univariable analysis for AKI in patients with Leukemia undergoing allogeneic HSCT.

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 lines 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
Conditioning Regimen (reference category non myeloablative)	1.27	0.84	1.95	0.26
Donor (reference category related donor)	0.99	0.67	1.46	0.94
Graft source (reference category peripheral blood)	1.47	0.68	0.86	0.16
GVHD prophylaxis (reference category not methotrexate)	1.27	0.84	1.95	0.26
Time to engraftment (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/ VOD	1.73	0.75	4	0.2
At hospital admission day:				
Hemoglobin (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 12 - BMI - body mass index; RIC (reduced-intensity regimen); HCT CI - hematopoietic stem cell transplant comorbidity index; HSCT - hematopoietic stem cell transplant; AML – Acute Myeloid Leukemia; ALL – Acute Lymphoblastic Leukemia; CML - Chronic Myeloid Leukemia; ICU - intensive care unit; GVHD - Graft versus Host Disease during hospital stay for HSCT; CMV – cytomegalovirus; TMA/ TLS/ VOD – Thrombotic microangiopathy/Tumor Lysis Syndrome/ Veno-occlusive disease.*

Variables independently associated with a higher incidence of AKI are shown in Table 13 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).

Table 13 Multivariable analysis for AKI in patients with Leukemia undergoing allogeneic HSCT.

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

*Legend table 13 - HCT CI - hematopoietic stem cell transplant comorbidity index; LDH – Lactate dehydrogenase; *considering each 1000 units/L increment*

Impact of AKI on overall survival and relapse-free 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)

Analyzing 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 14.

Table 14 Multivariable analysis for mortality in patients with Leukemia undergoing allogeneic HSCT.

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	2.00	6.95	<0.001
Severe AKI in the first 100 days of HSCT	1.76	1.03	3.00	0.037
Shock	4.48	2.84	7.06	<0.001
Relapse in the first 13 months of HSCT	2.00	1.33	3.02	0.001
Relapse after 13 months of HSCT	14.39	5.92	34.99	<0.001

Legend table 14 - LDH – lactate dehydrogenase; AKI – Acute Kidney Injury; HSCT – Hematopoietic Stem Cell Transplant

Accordingly, patients with severe AKI had almost a double risk (HR:1.76, 95% CI:1.03-3.00) (Figure 7), shock was associated with approximately a four-fold risk of mortality (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).

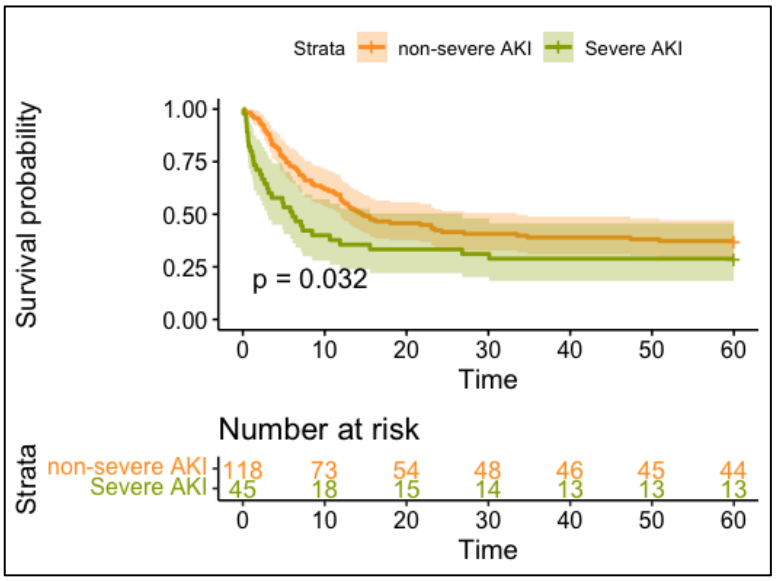


Figure 7 Overall survival and AKI in Leukemia undergoing allogeneic HSCT

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).

Impact of AKI on CKD and loss of renal function

The CKD incidence previous to HSCT was 3% and their median eGFR was 115 (100-130) mL/min/1.73 m2. At the end of the follow up, CKD incidence was 11% and eGFR reduction superior to 25% was registered in 27% of the patients. No association was found between CKD and AKI (p= 0.605) and eFGR reduction and AKI (p=0.450).

4.4 Predictive risk score for patients undergoing HSCT

Population description

Five hundred and thirty-four patients underwent HSCT at CHULN, EPE between January 2005 and December 2015. Among these patients, one hundred and twelve patients were excluded for presenting at least one exclusion criteria and 422 patients were eligible for the study.

Patients' baseline characteristics and transplant-related aspects are shown in Table 15.

Table 15 Patients' baseline characteristics and transplant-related variables for all patients undergoing HSCT.

Patients Characteristics	Category	n (%)	P50 (P25-75)
Age at transplant (years)			50.2 (36.0 - 59.5)
Gender	Male	236 (55.9)	
Race	Caucasian	385 (91.4)	
BMI (Kg/m2)			24.6 (21.9 - 27.8)
HCT-CI	0-1	353 (84.3)	
	≥2	66 (15.8)	
Hypertension		88 (20.9)	
Diabetes Mellitus		26 (6.2)	
Congestive Heart Failure		23 (5.5)	
Chronic Kidney Disease		27 (6.4)	
Hematologic Diagnosis	Leukaemia	164 (38.8)	
	Lymphoma	115 (27.3)	
	Multiple Myeloma	143 (33.9)	
Type of HSCT	Autologous	258 (61.1)	
	Allogeneic	164 (38.9)	
Type of donnor	Self	258 (61.1)	
	Related	92 (21.8)	
	Not related	72 (17.1)	
Previous radiotherapy	yes	82 (19.5)	
basal eGFR (ml/min/1,73m2)			107.3 (94.3 - 122.1)
Conditioning Regimen	Myeloablative	305 (72.2)	
	Non-myeloablative	117 (27.8)	
Graft source	perihperal blood	389 (92.2)	
	bone marrow	33 (7.8)	
GVHD prophylaxis	CsA + MMF	117 (27.7)	
	CsA + MTX	47 (11.1)	
	None	258 (61.1)	
At hospital admission day:			
Hemoglobin (gr/dl)			11.6 (10.2 - 12.6)
Leukocytes (cells/mm3)			4920 (3500 - 6860)
Neutrophils (cells/mm3)			2960 (1850 - 4420)
Platelets (/µl)			179000 (127000 - 245000)
Urea (mg/dl)			33 (27 - 41)
Uric Acid (mg/dl)			5.2 (4.0 - 6.0)
Calcium (mg/dl)			9.2 (8.8 - 10.0)
Phosphate (mg/dl)			3.6 (3.2 - 4.1)
Reactive C Protein (mg/dl)			0.49 (0.15 - 2.00)
Lactate Dehydrogenase (U/L)			339 (291 - 426)
Albumin (mg/dl)			4.0 (3.7 - 4.5)
Alanine Transaminase (U/L)			22 (15 - 37)
Total Bilirubin (mg/dl)			0.48 (0.36 - 0.61)
Platelet-to-lymphocyte ratio			159.9 (94.1 - 265.4)

Legend table 15 - SD – Standard deviation; P50 – median; P25 – 25th percentile; P75 – 75th percentile; BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; eGFR – estimated glomerular filtration rate;Nr – number.

Cumulative incidence of AKI

The AKI cumulative incidence was 59.1 % at 100 days after autologous HSCT. Figure 8.

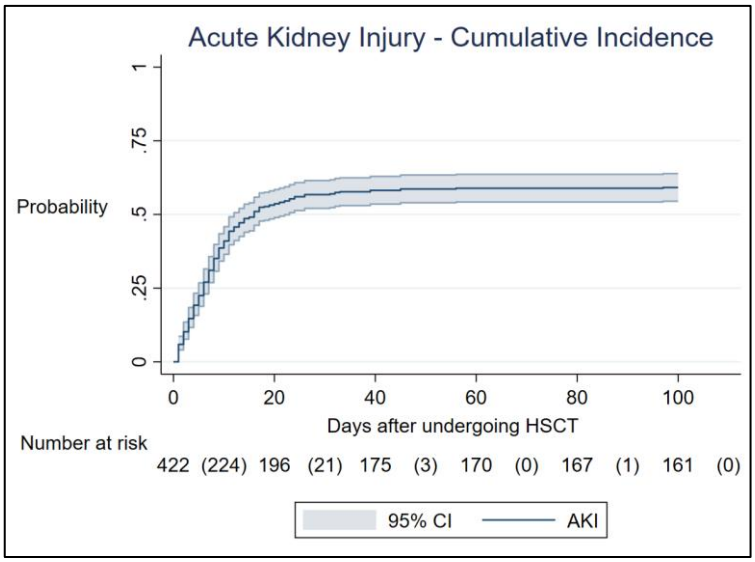


Figure 8 AKI cumulative incidence in all patients undergoing HSCT.

HSCT – Hematopoietic Stem Cell Transplant; CI – Cumulative Incidence; AKI – Acute Kidney Injury.

Variable analysis and predictive score for AKI

In the univariable analysis performed for AKI considering death as a competing event the variables associated with AKI in this analysis were: HCT-CI≥2, Chronic Kidney Disease, Hematologic diagnosis – Leukemia or Lymphoma, basal eGFR, Leukocytes count at admission, Lymphocytes count at admission; Reactive C Protein at admission, Lactate Dehydrogenase at admission and Platelet-to-lymphocyte ratio at admission. Each variable with its respective Hazard Ratio, confidence interval, and p-value is shown in Table 16 .

Table 16. Univariable analysis for AKI including variables available before the HSCT

Patient's Characteristics	HR estimate	95% CI		p-value
		lower limit	upper limit	
Age at transplant (years)	1.00	0.99	1.01	0.830
Gender (reference cathegory female)	1.05	0.83	1.35	0.654
Race (reference cathegory caucasian)	0.9	0.58	1.40	0.634
BMI (Kg/m2)	1.02	1.00	1.05	0.105
HCT-CI (reference cathegory <2)	1.69	1.27	2.25	<0.001
Hypertension	1.15	0.86	1.54	0.335
Diabetes Mellitus	1.29	0.82	2.02	0.269
Congestive Heart Failure	1.41	0.91	2.20	0.128
Chronic Kidney Disease	2.11	1.36	3.27	0.001
Hematologic Diagnosis:				
Multiple Myeloma versus Lymphoma	1.51	1.10	2.08	0.011
Multiple Myeloma versus Leukemia	1.44	1.07	1.92	0.015
Leukemia versus Lymphoma	1.05	0.78	1.41	0.728
Multiple Myeloma versus (Lymphoma + Leukemia)	1.46	1.12	1.90	0.005
Type of HSCT (reference cathegory allogeneic)	0.84	0.66	1.08	0.169
Type of donor (reference cathegory related)	1.14	0.86	1.52	0.368
Previous radiotherapy	1.09	0.81	1.47	0.573
Conditioning regimen (reference cathegory non-myeloablative)	1.27	0.84	1.95	0.260
basal eGFR (ml/min/1,73m2)	0.99	0.99	1.00	0.012
Graft source (reference cathegory perihperal blood)	1.36	0.88	2.12	0.170
GVHD prophylaxis (reference cathegory methotrexate)	1.03	0.73	1.46	0.849
At hospital admission day:				
Hemoglobin (gr/dl)	1.01	0.94	1.09	0.752
Leukocytes (cells/mm3)	1.00	1.00	1.00	<0.001
Neutrophils (cells/mm3)	1.00	1.00	1.00	0.547
Lymphocytes (cells/mm3)	1.00	1.00	1.00	<0,001
Platelets (/µl)	1.00	1.00	1.00	0.841
Urea (mg/dl)	1.01	1.00	1.02	0.019
Uric Acid (mg/dl)	1.01	0.97	1.04	0.662
Calcium (mg/dl)	1.06	0.85	1.31	0.598
Phosphate (mg/dl)	0.92	0.77	1.10	0.367
Reactive C Protein (mg/dl)	1.00	1.00	1.00	<0.001
Lactate Dehydrogenase (U/L)	1.00	1.00	1.00	<0.001
Albumin (mg/dl)	1.00	0.96	1.04	0.847
Alanine Transaminase (U/L)	1.00	0.99	1.00	0.081
Total Bilirubin (mg/dl)	0.91	0.62	1.32	0.611
Platelet-to-lymphocyte ratio	1.00	1.00	1.00	<0.001

Legend table 16 - BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; Nr – number; HSCT – Hematopoietic stem cell transplant; eGFR – estimated glomerular filtration rate; GVHD – grafts versus host disease;

Considering only variables of Table 2 with p<0.200 and applying the Liu index to establish the optimal cut-off point for each variable, the variables associated with AKI in the univariable analysis were: HCT-CI≥2, chronic kidney disease, and

Hematologic diagnosis – Leukemia or Lymphoma. Each variable with its respective Hazard Ratio, confidence interval, and p-value are presented in Table 17.

Table 17 Univariable analysis for AKI including the selected variables in table (anterior) after applying the Liu index and establishing the optimal cut-off point.

Patient's Characteristics	HR estimate	95% CI		p-value
		lower limit	upper limit	
BMI (>24.5 Kg/m2)	1.2	0.94	1.53	0.147
HCT-CI (reference cathegory <2)	1.69	1.27	2.25	<0.001
Congestive Heart Failure	1.41	0.91	2.2	0.128
Chronic Kidney Disease	2.11	1.36	3.27	0.001
Hematologic Diagnosis (reference cathegory Multiple Myeloma)	1.46	1.12	1.91	0.005
Type of HSCT (reference cathegory allogeneic)	0.84	0.66	1.08	0.169
basal eGFR (>107.2 ml/min/1,73m2)	0.89	0.7	1.13	0.342
Graft source (reference cathegory perihperal blood)	1.36	0.88	2.12	0.170
Leukocytes (>5330 cells/mm3)	1.05	0.82	1.34	0.696
Lymphocytes (>1100 cells/mm3)	0.89	0.7	1.13	0.334
Urea (>30 mg/dl)	1.15	0.9	1.48	0.263
Reactive C Protein (>0.47 mg/dl)	1.2	0.92	1.55	0.176
Lactate Dehydrogenase (>339 U/L)	1.26	0.98	1.61	0.066
Alanine Transaminase (>22 U/L)	1.02	0.8	1.31	0.853
Platelet-to-lymphocyte ratio (>171.9)	1.26	0.97	1.62	0.078

Legend table 17 - BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; HSCT – Hematopoietic stem cell transplant; eGFR – estimated glomerular filtration rate;

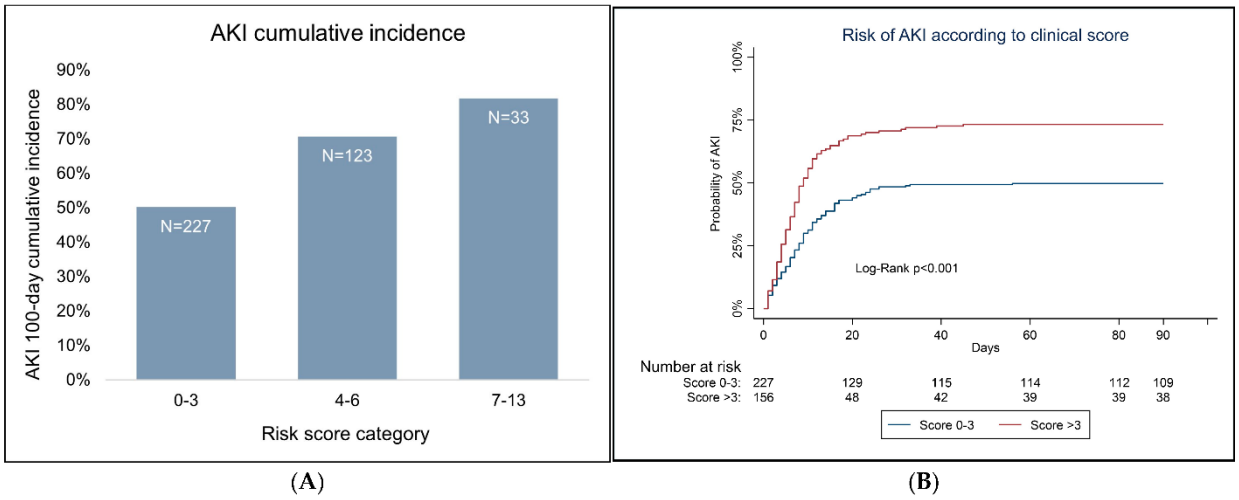
In multivariable analysis, variables with independent association with AKI were: HCT-CI≥2 (HR:1.47; 95%CI:1.08-2.00; p=0.013), Chronic Kidney Disease (HR:2.10; 95%CI:1.31-3.36; p=0.002), Hematologic diagnosis – Leukemia or Lymphoma (HR:1.69; 95%CI:1.31-3.36; p=0.002), and Platelet-to-lymphocyte ratio > 171.9 (HR:1.43; 95%CI:1.10-1.86; p=0.008) (Table 18).

The attributable score points to each variable are also shown in Table 18. AKI cumulative distribution by score is shown in Figure 9. For a score >3, there was a higher unadjusted risk of incident AKI at 100 days of follow-up (Log-Rank <0.001), with an AKI probability of 75.6% [95% CI 82% - 68.7%] (N day 0 = 227, N day 100 = 107), while patients with a score 0-3 presented a probability of 47.2% [40.5% - 53.5%] (N day 0 = 156, N day 100 = 38).

Table 18 Multivariable analysis for AKI in HSCT with Score points.

Patient's Characteristics	HR estimate	95% CI		p-value	Score Points
		lower limit	upper		
HCT-CI (reference category <2)	1.47	1.08	2.00	0.013	**3**
Chronic Kidney Disease	2.10	1.31	3.36	0.002	**4**
Hematologic Diagnosis (reference category Multiple Myeloma)	1.69	1.26	2.25	<0.001	**3**
Platelet-to-lymphocyte ratio (reference category <171.9)	1.43	1.1	1.86	0.008	**3**
Multivariable model C-Statistic = 0,71					
Score C-Statistic = 0,70					

HCT-CI - hematopoietic stem cell transplant comorbidity index.



(A) (B)

Figure 9 (A) AKI cumulative incidence at 100 days according to different score categories. (B) AKI distribution curves by score category (score 0-3 and score <3).

Chapter 5 - Discussion

We organized our discussion according to the questions that this project aimed to answer.

What is the incidence, presentation criteria and severity of AKI in patients undergoing HSCT considering different hematologic malignancies?

Cumulative incidence

In all our studies, we used the most updated AKI definition—the KDIGO definition—including both serum creatinine criteria and urinary output criteria in order to calculate the cumulative incidence of AKI. We considered the first 100 days after HSCT as a timeline, and we followed the same statistical approach as suggested by the European Group for Blood and Marrow Transplantation guidelines on statistical methodology published in 2013 [88]. In our analysis of patients with multiple myeloma undergoing autologous HSCT, we found an AKI cumulative incidence of 49.7%; in our analysis of patients with lymphoma undergoing autologous HSCT, we registered an AKI cumulative incidence of 63.7%; and in our analysis of patients with leukemia undergoing allogeneic HSCT, the cumulative AKI incidence was 63.4%. The analysis of all the above hematologic diagnoses and both types of transplants showed an AKI cumulative incidence of 59.1%.

These results show different AKI cumulative incidences using the same methodology when approaching different hematologic malignancy groups individually, reinforcing the idea that the burden of the hematologic diagnosis and respective previous treatments may influence AKI incidence. Despite the fact that many authors have previously suggested that autologous HSCT has lower AKI incidences compared to allogeneic HSCT, our results question this assumption: although multiple myeloma undergoing autologous HSCT registered the lowest incidence, lymphoma undergoing autologous HSCT registered a slightly higher incidence than leukemia undergoing allogeneic HSCT, could it be because in other studies patients with multiple myeloma and lymphoma were included and analyzed

in the same category as autologous HSCT and multiple myeloma contributed to more patients than lymphomas, shifting the incidences to lower results?

Thus, comparing our results with the literature is challenging because our studies are the only ones that consider urinary output criteria for AKI (which, as a criterion inserted in the most updated definition of AKI, we believe contributes to more accurate results), and there are very few studies focusing on specific hematologic malignancies in their analysis.

Considering the data available on autologous HSCT in general, Caliskan et al. (2006) reported an AKI incidence of 52% [91]. In studies on autologous HSCT in particular populations, Fadia et al. (2003) reported a moderate-to-severe AKI incidence (defined by more than 1 mg/dL increase in serum creatinine or a doubling of serum creatinine to more than 1.5 mg/dL for at least 2 days) of 21% [92] in a population with AL amyloidosis. Merouani et al. (1996) reported an AKI incidence (defined by a decrement in GFR superior to 25%) of 56% [93] in a population with breast cancer. Andronesi et al. (2019) reported an AKI incidence (KDIGO classification through creatinine criteria) of 10.4% in the first 30 days of HSCT [79] in a population with multiple myeloma.

Comparing these results with our study on multiple myeloma patients undergoing autologous HSCT (AKI cumulative incidence of 49.7% and moderate-to-severe AKI cumulative incidence of 14.1%), we were already expecting to have lower moderate-to-severe AKI incidence in our study compared to the AL amyloidosis population study (even considering different definitions for AKI), as the presence of amyloidosis was itself an independent risk factor for AKI in our study. Also, we were also expecting to have a lower AKI incidence compared to populations with breast cancer, where HSCT is performed in patients with advanced-stage, uncontrolled disease needing high-dose chemotherapy and where the performance of autologous HSCT is not a first-line procedure, considering that autologous HSCT in multiple myeloma is a first-line therapy normally performed as a consolidation therapy after the remission or at least partial response to pre-transplant therapy has been achieved, resulting in a lower treatment and disease burden compared to other

diseases. We believe our higher AKI incidence compared to Andronesi et al.'s multiple myeloma population can be explained by the fact that we included not only serum creatinine criteria but also urinary output criteria. We considered an incidence period of 100 days after HSCT instead of the 30 days referred to in their study, and our population was older.

Comparing the AKI incidences in the above-mentioned autologous HSCT studies (including our multiple myeloma results) with our study on lymphoma patients undergoing autologous HSCT, the AKI incidence was much higher in patients with lymphoma undergoing autologous HSCT (cumulative incidence of AKI of 63.7% and moderate-to-severe AKI of 27.1%). The fact that patients with lymphoma are generally younger and have a lower incidence of other cardiovascular risk factors such as diabetes, hypertension, or chronic kidney disease could foresee a lower risk for AKI, but patients with lymphoma are often exposed to high-dose chemotherapy regimens that are related to higher nephrotoxicity, and the performance of HSCT is often used when the disease relapses or progresses despite chemotherapy regimens. We believe that this exposure to high-dose chemotherapy regimens, often nephrotoxic, and a relapsed or refractory setting at the time of HSCT, resulting in a higher disease burden, can be in part responsible for the higher AKI incidence, not excluding the possibility of the contribution of lymphoma-related factors yet to be discovered.

More data is available considering allogeneic HSCT in general compared to autologous HSCT in general. Parikh et al. (2005) presented a 59% incidence of creatinine-doubling in allogeneic HSCT [94]; Lopes et al. (2006) showed a 27% creatinine-doubling in allogeneic HSCT (Lopes JA, Jorge S, Silva S, Almeida E de, Abreu F, Martins C, et al. Acute renal failure following myeloablative autologous and allogeneic hematopoietic cell transplantation Bone Marrow Transplant. 2006 Nov;38([10]):707–707. Mori et al. (2012) presented 62% incidence in AKI by AKIN in allogeneic HSCT[95]. Recent studies applied part of the AKI KDIGO classification using only creatinine criteria, and some even considered weekly measurements. Gutierrez-Garcia et al. (2020) presented a 63.4% AKI incidence when considering

weekly serum creatinine measures [76], and Andronesi et al. (2022) showed a 68.9% AKI incidence [77].

Comparing the AKI incidences in the above-mentioned allogeneic HSCT studies (including our multiple myeloma results) with our study on leukemia patients undergoing allogeneic HSCT, the AKI incidence is similar (cumulative incidence of AKI of 63.7% and moderate-to-severe AKI of 27.1%) to the studies considering KDIGO classification. We would be expecting a higher incidence in our study considering that we also used urinary output criteria for the AKI diagnosis. One reason for that could be that all the other studies included not only patients with leukemia (like we did), who are often submitted to allogeneic HSCT as first-line therapy after chemotherapy has provided disease remission, but also patients with other hemato-oncological diseases, such as multiple myeloma and lymphoma, where indication for allogeneic HSCT comes after long periods of chemotherapy with a higher burden of immunosuppression, often with nephrotoxic drugs, and in most cases, previous autologous HSCT that has failed to treat the underlying disease.

The distribution of AKI incidence along the 100 first days after HSCT in our studies (shown in the cumulative incidence figures on each population) points to a significantly higher incidence in the first 40 days, with almost all cases of AKI in the autologous HSCT population and the large majority of the allogeneic HSCT population occurring during this period, a lower incidence between 40 and 60 days after HSCT, and very few cases occurring after that period. This finding should raise awareness for clinical practice during the first half of the 100 days.

Presentation criteria

Although creatinine elevation (alone or along with urinary output reduction) was the first criteria for AKI in the majority of the patients in all our studies, urinary output reduction alone was the first AKI diagnostic criteria in 18.3% of AKI patients with multiple myeloma undergoing autologous HSC, in 41.1% of AKI patients with lymphoma undergoing autologous HSCT, and in 15.4% of AKI patients with

lymphoma undergoing allogeneic HSCT. Considering the three study populations together, 24.9% of all AKI diagnoses were made first by a detectable urinary output reduction alone.

KDIGO guidelines and bundles of care for AKI treatment continue to be limited and mostly supportive. The 2019 Acute Disease Quality Initiative (ADQI) conference on "Quality Improvement for AKI" [96] proposed that the range of care in AKI should be a continuum from risk assessment, prevention, and early diagnosis to optimizing AKI management, and finally to the surveillance of AKD and the prevention of recurrent AKI and progression to CKD. Thus, early diagnosis is crucial, leading to an earlier identification of the cause (or causes) and an attempt to reverse them in time to stop AKI progression. We believe that our observation of urinary output reduction alone earlier than creatinine rise (creatinine rise alone or creatinine rise in the same day of urinary output reduction) in 25% of AKI patients is extremely important because it reinforces a diagnostic tool that has not been taken into consideration by other authors and can provide better care in a quarter of these patients.

Severity

In our studies concerning different populations, we observed the same trend considering the severity of AKI: more than eighty percent of patients with AKI presented with AKI stage 1 on the first day of AKI (85.9% of AKI patients with multiple myeloma, 80.8% of AKI patients with lymphoma, and 80.8% of AKI patients with leukemia), but moderate-to-severe AKI was reached along the episode by 28.2% of AKI patients with multiple myeloma, 42.5% of AKI patients with lymphoma, and 38.6% of AKI patients with leukemia.

Considering the impact of AKI on short-term and long-term outcomes in different AKI scenarios, it is known that worse results are directly related to the severity of acute kidney injury, whether characterized by nominal or percentage changes in serum creatinine [45]. In HSCT populations in particular, most studies (including the studies

performed for this project) concluded that there was a statistically significant impact of more severe stages of AKI on overall survival.

Thus, considering that we assisted in the worsening of AKI severity in a substantial portion of patients, early diagnosis and a quick approach may reduce the probability of progression to more severe stages and, consequently, improve outcomes. This assumption needs more studies to be proven, though we believe this reinforces once more the importance of urinary output monitorization (as exposed in the "presentation criteria" subsection of this chapter) as well as the need for a predictive risk score.

What are the risk factors for AKI in patients undergoing HSCT considering different hematologic malignancies?

In our study concerning multiple myeloma patients undergoing autologous HSCT, AKI was independently associated with an HCT-CI score ≥ 2 points, mucositis grade 3–4, exposure to nephrotoxic drugs, a higher BMI, CKD, and the presence of amyloidosis. In our study, including patients with lymphoma undergoing autologous HSCT, AKI was independently associated with mucositis (any grade), exposure to nephrotoxic drugs, and an episode of shock. In our study of patients with leukemia undergoing allogeneic HSCT, AKI was independently associated with an HCT-CI score ≥ 2 points, an episode of sepsis, previous exposure to radiotherapy, shock, and LDH at hospital admission day for the procedure.

In our findings, some variables are consistent among the different populations and types of transplants, while others are specific to the hematologic disease. Most of the variables had shown previous associations with AKI in other studies (some in HSCT studies and others in AKI studies in other scenarios).

Considering patients´ characteristics and clinical background, BMI, HCT-CI score ≥ 2 points, and CKD were associated with AKI.

Higher BMI has been pointed out as a risk factor in other clinical settings by Gameiro et al. (2018) [97] and Billings et al. (2012) [98] in critically ill and septic patients and in

patients undergoing cardiac surgery, respectively. The association between BMI and AKI has been explained by the adipose production of inflammatory mediators (adipokines, leptin) and decreased production of adiponectin in response to acute illness, which increases susceptibility to AKI [99].

A score equal to or superior to 2 in the HCT-CI was associated with a higher risk of developing AKI in our studies in multiple myeloma patients undergoing autologous HSCT and in patients with leukemia undergoing allogeneic HSCT. This comorbidity index is validated for predicting non-relapse mortality and overall survival after HSCT based on 17 categories of pre-HSCT comorbidities and organ dysfunction [83]. This score was also pointed out as a risk factor for developing AKI in studies of AKI in allogeneic HSCT; the first author to mention it was Kagoya et al. (2011) [100], who by describing an association for AKI defined by the RIFLE classification in the first 100 days after allogeneic HSCT, showing an increase in risk between scores 0-1, 1-2, and ≥3. Recently, Vergara-Cadavid et al. (2023) described an increased risk of AKI in the first 30 days with HCT-CI ≥4 in their study comprising patients undergoing reduced-intensity conditioning (RIC) allogeneic HCT [101]. To our knowledge, we published the first study showing a relationship between the HCT-CI score and the risk for AKI in patients undergoing autologous HSCT. We believe these results enhance the impact of comorbidity burden in AKI in all HSCT scenarios, and they should be taken into consideration as an important prognostic tool not limited to survival prediction.

CKD conferred a more than twofold higher risk of developing AKI in our study of patients with multiple myeloma undergoing autologous HSCT and has also been referred to by Andronesi et al. (2019) [79] in the autologous HSCT population. In the last decade, CKD has been recognized as a clear risk factor for AKI in general [102], as it results in reduced renal reserve and an inability to handle stress such as abnormally low blood pressure or nephrotoxic drugs. We believe we did not register this statistically significant association in the other two studies because of the low incidence of CKD: among our patients with lymphoma, none had previous CKD, and among our patients with leukemia, only 3.6% had CKD prior to HSCT.

Considering the hematologic disease´s characteristics and treatment, the presence of amyloidosis, previous exposure to radiotherapy, and higher LDH before the conditioning regimen were associated with AKI.

The presence of amyloidosis in patients with multiple myeloma undergoing autologous HSCT was also associated with a higher risk of AKI. Renal deposition of amyloid reduces the capacity of the adaptive response to an insult, making the kidney more susceptible to acute kidney injury, and in more extreme cases, renal infarction has been registered. Also, patients may present with cardiac amyloidosis, predisposing them to cardiorenal syndrome [103] and thus making them more likely to develop acute kidney injury.

Total body irradiation was not performed on any of our patients, but patients with leukemia undergoing allogeneic HSCT who had been subjected to radiotherapy treatments in the past (including any corporal region at any time before HSCT) showed a higher incidence of AKI. Previous studies have shown an association between total body irradiation and AKI in allogeneic HSCT [104]. This finding corroborates experimental studies suggesting that exposure to radiation results in subclinical renal fibrosis that persists through time, making patients prone to AKI [105].

Patients with leukemia undergoing allogeneic HSCT who presented higher levels of LDH the day before the conditioning regimen had a higher incidence of AKI. LDH was mentioned by Geva et al. [106] as a key prognostic factor in acute myeloid leukemia and lymphoma patients undergoing allogeneic HSCT by showing an association between lactate dehydrogenase levels on the day before the conditioning regimen and death. Our results reinforce the importance of taking this marker into consideration as a surrogate for pre-transplant risk stratification, as we also found an independent association with AKI.

When transplant-related characteristics and complications are taken into account, sepsis, exposure to nephrotoxic drugs, mucositis, and shock are associated with AKI.

Although some studies did not find an independent association between sepsis and AKI in HSCT, in our study concerning patients with leukemia undergoing allogeneic HSCT, we confirmed this association. We were expecting this result considering the multiple interaction pathways between these two entities and their known association in other AKI scenarios, as well as the higher susceptibility to sepsis in HSCT given the immunocompromised state of these patients resulting not only from the induction regimens but also from the chronic inflammatory state related to the hematologic disease itself. This finding was also mentioned by Liu et al. [107] and Andronesi et al. [77], who reported an association between sepsis and AKI stage 3 in allogeneic HSCT.

Exposure to nephrotoxic drugs had an expected significantly higher incidence in patients with AKI, in our patients with lymphoma undergoing autologous HSCT, and in our patients with multiple myeloma undergoing autologous HSCT. This result has been consistently suggested in other studies [93] [108] [109]. Unfortunately, these patients were often treated with multiple nephrotoxic drugs at the same time, making it impossible to identify the individual contribution of each drug to AKI.

Our studies with patients with lymphoma and patients with multiple myeloma undergoing autologous HSCT reported an association of mucositis with a higher AKI incidence. This finding was also mentioned by Andronesi et al. [79] in autologous HSCT studies and is explained mainly by the extracellular volume depletion as a consequence of vomiting and diarrhea.

We did not find other associations for AKI in our studies, although some authors mention other risk factors. For instance, in our study of patients undergoing allogeneic HSCT, patients submitted to a myeloablative conditioning regimen did not have a statistically significant higher AKI incidence compared to patients submitted to a non-myeloablative conditioning regimen. Although Parikh et al. (2005) and other studies reached statistical significance comparing non-myeloablative regimens to myeloablative regimens [94], our results are shared by Mori et al. (2012) on their work with allogeneic HCT patients [95] and are also referred to by JA Lopes et al. (2016) [110]. Considering that the decision between non-myeloablative regimens and

myeloablative regimens is made according to the performance status of the patient, we believe that patients undergoing non-myeloablative regimens already have other comorbidities that could be responsible for a higher AKI risk that could surveil the eventual protective effect of a non-myeloablative regimen over AKI.

What is the prognostic impact of developing AKI during the first 100 days after HSCT in patients undergoing HSCT, considering different hematologic malignancies?

AKI in more severe stages had a negative prognostic impact on overall survival in all our studies. In patients with multiple myeloma undergoing autologous HSCT, moderate to severe AKI was independently associated with lower overall survival (HR: 1.62, 95% CI: 1.15–1.31), along with diabetes mellitus, a higher BMI, the presence of cytogenetic abnormalities, and disease relapse. In patients with lymphoma undergoing autologous HSCT, moderate to severe AKI was independently associated with lower overall survival (HR: 2.04, 95% CI: 1.06-3.94; p = 0.033), along with higher BMI and disease relapse. In patients with leukemia undergoing allogeneic HSCT, severe AKI was independently associated with lower overall survival (HR: 1.76, 95% CI: 1.03–3.00; p =0.037), along with shock, relapse, leucocyte count, and LDH the day before the conditioning regimen.

The impact of AKI on overall survival was not consistently found in HSCT studies. Andronesi et al. (2019) [79] did not find higher mortality rates in autologous HSCT with AKI, including all stages. But the majority of the studies considering HSCT in general have demonstrated that mortality rates increase as the severity of AKI increases [94] [111]. In fact, a meta-analysis by Kanduri et al. (2020) [75] on the matter concluded an impact on 3-month mortality and 3-year mortality, with a higher impact in more severe stages. We believe this conclusion is reinforced by our studies with even longer follow-up. Also, by observing that the stage at the onset of AKI was not always the highest stage reached during AKI episodes, we reinforce the need for an earlier diagnostic and therapeutic approach.

We did not find an association between AKI at any stage and relapse-free survival. Our results were consistent with most of the studies, but Madsen et al. (2022) [78] describe a significant impact on relapse-free survival, although there is no difference in the 2-year incidence of relapse, in a population undergoing allogeneic HSCT.

We evaluated the relationship of AKI with CKD or eGFR reductions greater than 25% at the end of the follow-up period. In multiple myeloma patients undergoing autologous HSCT, although a reduction in eGFR was observed in 32.1% and CKD prevalence rose from 10% to 27.5%, we did not find a statistically significant association with AKI. In lymphoma patients undergoing autologous HSCT, eGFR reduction superior to 25% was registered in 31.8% of the patients, and CKD prevalence rose from non-existent to 2.2%, also with no association with AKI during the first 100 days of HSCT. In leukemia patients undergoing allogeneic HSCT, a reduction in eGFR was observed in 27% of the patients, and CKD prevalence rose from 3% to 11%, but we still did not find a statistically significant association with AKI.

According to our knowledge of the AKI impact on CKD in other clinical settings [112], we would expect a statistically significant association in our studies. But Gutierrez-García et al. (2020) [76] and Sakagushi et al. (2020) [113] also failed to find this association in their studies on allogeneic HSCT recipients. Sakellari et al. (2013) [65] reported an association between AKI and CKD in HSCT but defined CKD as eGFR < 90 ml/min/1.73 m2 and used an outdated AKI definition. These findings may suggest other risk factors specific to HSCT for CKD, overlapping the AKI association with CKD in this setting.

In fact, in all our studies on CKD, an eGFR reduction was superior to what was expected when compared to the general population. The median eGFR prior to the HSCT was superior to 100 ml/min/1.73 m2, and eGFR reductions superior to 25% occurred in more than a quarter of the patients. The expected reduction in eGFR is 1 ml/min/m2 per year beginning in the third decade of life [114]. Considering our 5-year follow-up period, the registered reduction in the HSCT population is alarming.

We believe that more studies on the impact of the HSCT itself on CKD are necessary.

Is it possible to predict the risk for AKI in patients undergoing HSCT?

The high incidence of AKI in our studies and its progression to a moderate-to-severe stage that is related to lower overall survival make the possibility of detecting patients at increased risk a clinical need.

Although many AKI risk factors occurring in the first days after HSCT have been identified, we built a predictive risk score for AKI in patients undergoing HSCT based on 422 patients, including only variables available before this procedure is performed. By doing so, we assure a predictive risk score applicable at the beginning of the hospital stay that does not need to be repeated or updated during the following days, which we believe also facilitates the clinician's compliance.

Our predictive risk score takes into consideration the presence of chronic kidney disease prior to HSCT, the HCT-CI score, the platelet-to-lymphocyte ratio at admission, and the hematologic malignancy diagnosis. All these variables are consistent with previous literature on AKI risk factors, except for the platelet-to-lymphocyte ratio, which has been recently associated with lower overall survival in several oncologic scenarios and is mentioned in this AKI prediction context for the first time.

Chronic kidney disease is an extensively known risk factor for AKI [115]. As already mentioned in this discussion section, chronic kidney disease results in a state of constant relative hypoxia with reduced numbers of peritubular capillaries, increased deposition of collagen, myofibroblast proliferation, increased activation of the renin-angiotensin system, and reduced numbers of glomeruli, leading to hyperfiltration and higher tubular oxygen consumption of the corresponding tubules [116]. These aspects, combined with the chronic leukocyte infiltration and pro-inflammatory environment of chronic kidney disease, result in reduced renal reserve and maladaptation, loss of autoregulation, and abnormal vasodilation, which represent

perfect conditions for enhanced susceptibility to developing AKI. The independent association between an HCT-CI score higher than 2 points and AKI underscores the importance of previous comorbidities in the context of AKI. HCT-CI is already calculated in the majority of centers that perform HSCT because it provides information about the overall and non-relapse mortality risk a patient is likely to experience after HSCT. Its application as a predictor for AKI is thus facilitated by its already worldwide use.

Platelet-to-lymphocyte ratio is a novel inflammatory marker revealing shifts in platelet and lymphocyte counts due to acute inflammatory and prothrombotic states that has been used in several clinical contexts for predicting inflammation and mortality. It is calculated by dividing platelet count by lymphocyte count, which makes it a simple, inexpensive, and rapid marker. It has been associated with worse overall survival in various solid tumors [117], with higher mortality in patients with acute heart failure [118], in septic patients [119], and in patients with rheumatic diseases [120]. An association has also been reported between the platelet-to-lymphocyte ratio and the worse prognosis of septic AKI patients [121]. Considering that this ratio includes two results that are easily assessed and that are included in every laboratorial admission panel, this variable is unexpensive and available to all the clinicians.

Another variable included in our model is the hematologic diagnosis. In our studies, patients with Multiple Myeloma had a statistically significant lower risk of developing AKI compared to patients with either Lymphoma or Leukemia. As we already exposed in this section, we believe this aspect may be related to the lower treatment burden prior to HSCT in patients with Multiple Myeloma and also the oncologic status, as multiple myeloma patients must be in remission for HSCT, and this procedure is part of first-line treatment. In contrast, patients with Lymphoma or Leukemia are often exposed to high-dose chemotherapy regimens several times before de-HSCT and are transplanted in a relapsed or refractory setting.

Unlike most studies on AKI in HSCT (and on AKI in general), we used both creatinine and urinary output criteria for the KDIGO classification. This aspect contributes to a

more accurate diagnosis of AKI and, consequently, a higher precision and internal validity of our results. The fact that we only used variables available at the time of hospital admission allows the score to be calculated at a single point in time and before undergoing HSCT, which makes it more user-friendly. The inclusion of patients undergoing both autologous and allogeneic HSCT allows the application of this predictive risk score to a wider HSCT population. Also, our score was created based on clinical characteristics and laboratory results that are easily assessed, inexpensive, and are currently part of the evaluation of every patient eligible for HSCT in all countries that offer this procedure. This aspect makes this score accessible to all clinicians at no additional cost.

Our model provides novelty in two aspects: 1) by being to the best of our knowledge the first study proposing a predictive risk score for AKI in patients undergoing HSCT considering variables available at the time of hospital admission; 2) by being the first study to establish platelet-to-lymphocyte ratio as a risk factor for AKI.

We believe the introduction of this kind of tool in clinical practice is crucial, as it allows the implementation of preventive measures and earlier diagnosis in patients with a higher risk of developing a complication known to have the worst prognostic impact on overall survival in this population.

Limitations

Our project was based on single-center data collection and a retrospective approach. These two aspects confer known limitations regarding data availability and external validity.

Considering the limitations on data availability, some aspects should be acknowledged. Sepsis was not possible to be defined by the updated definition because respiratory rate and partial pressure of CO2 were not available in the majority of patients. Patients often had two or more nephrotoxic drugs prior to AKI, which does not allow for the extraction of exact information on which nephrotoxic had a higher impact on AKI. Also, other criteria for CKD, like proteinuria or structural

abnormalities, were not available, as were other serum creatinine measures between 1 year and 3 years after HSCT.

Although this project included 422 patients, which represents a significantly higher number of patients compared to most studies on this population, some known risk factors in other populations for AKI, such as shock, are represented by a very small number.

Also, the score was developed and tested in the same group of patients, which might have overestimated its overall performance. It is expected that its C-statistic should be different in other clinical cohorts.

To overcome these limitations, more studies are needed in this population of patients defining AKI by KDIGO classification through both creatinine and urinary output criteria, particularly large, prospective and multicentric studies.

Chapter 6 - Conclusions and Future Perspectives

This project aimed to fill a gap in the knowledge of AKI in hemato-oncologic patients undergoing HSCT – the epidemiologic evaluation of this entity in each hematologic malignancy group considering the KDIGO classification including both creatinine and urinary output, and the creation of a predictive risk score for these patients. The considered groups included multiple myeloma patients undergoing autologous HSCT, lymphoma patients undergoing HSCT, and leukemia patients undergoing allogeneic HSCT.

We concluded that AKI occurring in the first 100 days after HSCT calculated through this updated classification including both criteria had a cumulative incidence of 59.1% considering 422 patients with multiple myeloma, lymphoma, and leukemia undergoing either autologous or allogeneic HSCT for the first time. Patients with multiple myeloma undergoing autologous HSCT had an AKI cumulative incidence of 49.7%, patients with lymphoma undergoing autologous HSCT had an AKI cumulative incidence of 63.7% and patients with leukemia undergoing allogeneic HSCT had an AKI cumulative incidence of 63.4%.

Urinary output reduction alone was the first AKI diagnostic criteria in 18.3% of AKI patients with multiple myeloma, in 41.1% of AKI patients with lymphoma, and in 15.4% of AKI patients. Considering the three study populations together, 24.9% of all AKI diagnoses were made firstly by a detectable urinary output reduction alone.

We verified the same trend considering the severity of AKI in all groups: more than eighty percent of patients with AKI presented with AKI stage 1 on the first day of AKI, but moderate-to-severe AKI was reached as the AKI episode occurred in 28.2% of AKI patients with multiple myeloma, 42.5% of AKI patients with lymphoma, and 38.6% of AKI patients with leukemia.

Although there are some common risk factors, different hematologic diagnoses have different risk factors for AKI. The most significant risk factors for AKI in patients with multiple myeloma were an HCT-CI score ≥ 2 points, mucositis grade 3–4, exposure to nephrotoxic drugs, a higher BMI, CKD, and the presence of amyloidosis. In patients with lymphoma, the most important risk factors for AKI were mucositis (any grade), exposure to nephrotoxic drugs, and an episode of shock. In

patients with leukemia, the most important risk factors for AKI were an HCT-CI score ≥ 2 points, an episode of sepsis, previous exposure to radiotherapy, shock, and higher LDH levels the day before the conditioning regimen.

AKI in more severe stages had a negative prognostic impact on overall survival in all groups. In patients with multiple myeloma undergoing autologous HSCT and patients with lymphoma undergoing autologous HSCT moderate to severe AKI was associated with a reduction in overall survival and in patients with leukemia undergoing allogeneic HSCT this association was observed for patients who presented with severe AKI.

No association was found between AKI in any stage and relapse-free survival, CKD progression, or eGFR reductions greater than 25%.

We designed a predictive risk score for AKI in patients with hematologic malignancies undergoing HSCT, considering only inexpensive and easily accessible variables available before the procedure. Our score takes into consideration the presence of chronic kidney disease prior to HSCT, the HCT-CI score, the platelet-to-lymphocyte ratio at admission, and the hematologic malignancy diagnosis. To our knowledge, this is the first proposed predictive risk score for this population and the first association between platelet-to-lymphocyte ratio and AKI prediction.

We believe our project brings important knowledge to the epidemiologic information available on AKI in HSCT. By including urinary output criteria for the first time in the AKI diagnosis of this population, we believe to have increased the diagnosis accuracy and brought attention to the considerable percentage of cases in which this criterion alone is the first detectable change allowing earlier diagnosis and consequent earlier approach, which is a crucial aspect for stopping progression to more severe stages associated with worse outcomes. Also, we analyzed for the first time in the literature AKI in patients with lymphoma undergoing autologous HSCT separately from other hematologic diagnoses, and the other subgroups had very few studies with dedicated analyses. By analyzing groups separately according to the hematologic malignancy group and type of HSCT, we confirmed different risk factors for AKI for each group. This finding suggests that the hematologic diagnosis

and the burden of previous treatments may contribute to these differences and reinforces the need to perform more studies—prospective multicenter studies with a higher number of patients—approaching these groups separately in order to better understand AKI in the different scenarios. Also, although our score needs validation through multicenter prospective studies, we believe that by proposing the first predictive risk score for AKI in HSCT—especially one that is inexpensive and easy to calculate—we contribute significantly towards better clinical care for these patients. Considered the first pillar of the AKI approach in any scenario, with prediction comes prevention and early diagnosis, which is still the only treatment available for AKI

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Appendices

Appendix A. Rodrigues N., Branco C., Costa C., Marques F., Neves M., Vasconcelos P., et al., Acute kidney injury in autologous hematopoietic stem cell transplant for patients with lymphoma - KDIGO classification with creatinine and urinary output criteria: a cohort analysis. Ren Fail 2023. 45(1):2183044 DOI: 10.1080/0886022X.2023.2183044

Appendix B. Rodrigues N., Costa C., Branco C., Marques F., Vasconcelos P., Martins C., et al, 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. DOI: 10.47829/COO.2023.61801

Appendix C. Rodrigues, N.; Fragão-Marques, M.; Costa, C.; Branco, C.; Marques, F.; Vasconcelos, P.; Martins, C.; Leite-Moreira, A.; Lopes, J.A. Predictive Risk Score for Acute Kidney Injury in Hematopoietic Stem Cell Transplant. Cancers 2023, 15, 3720. https://doi.org/10.3390/cancers15143720

Appendix D. Rodrigues N., Costa C, Branco C, Martins C, Lopes J.A.. Acute Kidney Injury in Multiple Myeloma patients undergoing Autologous Hematopoietic Stem Cell Transplant – Cohort study. Submitted to Journal of Nephrology – under revision.

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CLINICAL STUDY

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Acute kidney injury in autologous hematopoietic stem cell transplant for patients with lymphoma – KDIGO classification with creatinine and urinary output criteria: a cohort analysis

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ABSTRACT

Eligibility and indication for autologous hematopoietic stem cell transplantation (HSCT) in patients with lymphoma are increasing. Acute kidney injury (AKI) is a known complication of HSCT with studies including a miscellaneous of hematological diagnoses and using different definitions of AKI. We aimed to evaluate incidence, risk factors and prognostic impact of AKI post-HSCT in patients with lymphoma submitted to autologous HSCT using the KDIGO classification with both serum creatinine and urinary output criteria. We performed a single-center retrospective cohort study including patients with lymphoma admitted for autologous HSCT. We used survival analysis with competing risks to evaluate cumulative incidence of AKI, AKI risk factors and AKI impact on disease-free survival. We used Cox regression for impact of AKI on overall survival. We used backward stepwise regression to create multivariable models. A total of 115 patients were included. Cumulative incidence of AKI: 63.7% 100 d post-HSCT. First diagnosis criteria: creatinine in 54.8%, urinary output in 41.1% and both in 4.1%. AKI highest stage: 1 in 57.5%, 2 in 17.8% and 3 in 24.7%. Variables independently associated with higher incidence of AKI were: use of nephrotoxic drugs (HR: 2.87, 95% CI: 1.07–7.65; $p = 0.035$), mucositis (HR: 1.95, 95% CI: 1.16–3.29; $p = 0.012$) and shock (HR: 2.63, 95% CI: 1.19–5.85; $p = 0.017$). Moderate to severe AKI was independently associated with lower overall survival (HR: 2.04, 95% CI: 1.06–3.94; $p = 0.033$). No association with relapse nor progression to chronic kidney disease (CKD) was found. AKI affects almost two thirds of patients with lymphomas submitted to autologous HSCT. Nephrotoxic drugs, mucositis and shock are important independent AKI risk factors. More than one third of AKI episodes are moderate to severe and these are associated with lower overall survival.

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Introduction

Over the last decades, we have witnessed an increase in the incidence of hematological malignancies and the development of new chemotherapy induction regimens. Hematopoietic stem cell transplantation (HSCT) has thus become an important therapeutic option for hemato-oncologic patients. Being consensually associated with significantly better survival rates in eligible patients, autologous HSCT is the most frequent and intensive approach for the treatment of lymphoma patients [1]. With a growing incidence of autologous HSCT in patients with lymphoma comes the necessity of better understanding complications and related clinical implications. Acute kidney injury (AKI) is an important complication in the first 100 d post HSCT in general, with studies showing an incidence ranging from 20 to 92% and a negative impact on overall survival [2–6]. These studies tend to include several hematological diagnoses submitted to different types of HSCT, as well as heterogeneous definitions for AKI not following more recent classifications and not accounting for urinary output.

AKI in autologous HSCT has been less studied than in allogeneic HSCT and include not only patients with lymphoma but also patients with multiple myeloma and/or amyloidosis, which have recognized different clinical characteristics and prognosis and may, in turn,

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result in less accurate data when extrapolating the results for each hematological diagnosis.

For the definition of AKI, the most updated and consensual classification is the KDIGO classification [7]. It 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 [8,9] (RIFLE and AKIN) to establish one classification of AKI for clinical practice, research and public health. To its full extent, it takes in consideration both serum creatinine elevation and urinary output reduction. Few recent studies on AKI in HSCT in general used the KDIGO classification and, even those, used only the creatinine elevation criteria for the KDIGO classification.

All these aspects enlighten the need for studies focusing on AKI in patients with lymphoma submitted to autologous HSCT, considering AKI definition by KDIGO whilst using both serum creatinine elevation and urinary output reduction.

Our study aims to 1) determine incidence and severity of AKI in patients with lymphoma submitted to autologous HSCT using KDIGO classification with both creatinine and urinary output criteria, 2) to identify independent risk factors for AKI in these patients and 3) to evaluate the impact of AKI on disease-free survival, on overall survival in the first 3 years after HSCT 4) To evaluate progression to chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) reduction superior to 25% at the end of the first year and at the end of the 3 years after HSCT.

Materials and methods

Study design, population, and data collection

We performed a single-center retrospective cohort study. Our study population included patients who were diagnosed with lymphoma and submitted to autologous HSCT at the Centro Hospitalar Universitário Lisboa Norte, EPE (CHULN) between January 2005 and December 2015. As exclusion criteria we defined: Patients under the age of 18 years, patients with CKD already on renal replacement therapy; patients who underwent renal replacement therapy one week before transplantation and those with previous HSCT.

The conditioning regimens used followed institutional protocols – Carmustine, Etoposide, Cytarabine and Melphalan (BEAM) or Thiotepa, Etoposide, Cytarabine and Melphalan (TEAM). Total body irradiation is not available in our institution, and it is not contemplated in any of our institutional protocols.

Our data collection was based on registers of daily medical records, 6-h period nurses' records and diagnostic exams during hospital admission period for HSCT, as well as all routine medical records and laboratorial analysis before and after HSCT. We collected variables related to patient demographic characteristics (age, gender, race, body weight, and height), related to patient comorbidities (diabetes mellitus, hypertension, arrythmia, valvular heart disease, ischemic heart disease, cerebrovascular disease, chronic liver disease, intestinal inflammatory disease, peptic ulcer, connective tissue disease, chronic obstructive pulmonary disease, and solid-organ cancer, psychiatric disease), related to lymphoma and previous treatment approach (subtype of lymphoma, number of previous lines of therapy, and exposure to radiotherapy in the past); related to HSCT (conditioning regimen, cells source, period of aplasia, length of stay in hospital, blood results on hospital admission day for HSCT, sinusoidal obstructive syndrome, thrombotic microangiopathy, sepsis, nephrotoxic drugs, shock, cytomegalovirus infection, AKI, and AKI stage) and related to prognostic impact (time to relapse, time to all-cause mortality and eGFR 1 year after HSCT and 3 years after HSCT).

All patients were followed until death or censored at 36 months (3 years) after HSCT. This timeline was defined because patients are often transferred to other hospitals closer to their residence for continued follow-up after this 3-year period.

Definitions

We considered serum creatinine at the last medical appointment before hospital admission for HSCT to be baseline serum creatinine. Baseline glomerular filtration rate was estimated according to CKD-EPI equation [10], using baseline serum creatinine.

AKI diagnosis was made based on daily values of serum creatinine and 6-h urinary output since the time of hospital admission for HSCT until hospital discharge, as well as all other hospital admissions or weekly evaluation in outpatient clinic in the first 100 d after HSCT. AKI was defined by KDIGO criteria [7] (any of the following: Increase in serum creatinine by $\geq$0.3 mg/dl ($\geq$26.5 µmol/l) within 48 h; or increase in serum creatinine to $\geq$1.5 times baseline, which is known or presumed to have occurred within the prior 7 d; or urinary output <0.5 ml/kg/h for 6 h). Stage of AKI followed KDIGO classification considering the worst serum creatinine value and/or longest period of urinary volume reduction during hospital stay for HSCT. Moderate to severe AKI was defined as AKI stage 2 and AKI stage 3.

CKD was defined as a persistent decrease in eGFR to below 60 ml/min/1.73 m^2, according to the definition of KDIGO [11].

The hematopoietic cell transplantation – specific comorbidity index (HCT-CI) [12] was calculated according to the latest validated version considering patients comorbidities. Shock was considered when patients presented with cardiac frequency >90 bpm, systolic blood pressure <90 mmHg, and at least one lactate determination >2 mmol/l or 22 mg/dl.

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

Ethical committee

This study was approved by the local Ethical Committee (approval number 35336) in agreement with institutional guidelines. Informed consent was waived by the Ethical Committee due to the retrospective and non-interventional nature of the study.

Statistical methods

Categorical variables were described as frequencies, continuous data were expressed as median and interquartile range (P25 = 25th percentile; P75 = 75th percentile).

We followed the statistical methodology suggested by the European Group for Blood and Marrow Transplantation [13]. We used survival analysis methods considering competing events – we considered death as a competing risk event – through the Fine and Gray method [14] to calculate cumulative incidence of AKI. We also used this survival analysis method to perform univariable and multivariable analyses of factors predicting AKI. We used backward stepwise regression to create the final multivariable model. This same strategy was applied to calculate the impact of AKI on disease-free survival. AKI impact on overall survival was evaluated using cox regression model followed by backward stepwise regression to create the final multivariable model. We considered type 1 right censoring for a period of three years after HSCT. We calculated the incidence of CKD and eGFR reduction >25% in survivors 1 year after HSCT and survivors 3 years after HSCT and evaluated association with AKI in the first 100 d post HSCT.

Analyses were performed with the statistical software package STATA version 16.0 for Windows (StataCorp, College Station, TX).

Results

One hundred and forty-three patients with lymphoma were submitted to autologous HSCT at our center between January 2005 and December 2015. Among these patients, 28 patients were excluded for presenting at least one exclusion criteria and 115 patients were eligible for the study. Patients' baseline characteristics and transplant-related aspects are shown in Table 1.

AKI cumulative incidence, presentation, and severity

The AKI cumulative incidence was 63.7% at 100 d after autologous HSCT (Figure 1).

The moderate-to-severe AKI cumulative incidence was 27.1% at 100 d after autologous HSCT.

The earlier diagnosis criteria for AKI were serum creatinine rise in 54.8% of patients and urinary output reduction in 41.1% of patients. Both serum creatinine rise and urinary output reduction were observed in the first day of AKI in 4.1% of patients.

In the first day of AKI, patients presented the following severity: AKI Stage 1 = 80.8%, AKI Stage 2 = 12.3%, and AKI Stage 3 = 6.9% (moderate-to-severe AKI in 19.2%). As AKI occurred, the highest severity registered was AKI Stage 1 = 57.5%, AKI Stage 2 = 17.8%, and AKI stage 3 = 24.7% (moderate to severe AKI in 42.5%).

AKI risk factors

In the univariable analysis, the predictor variables with impact on AKI were HCT-CI score ≥2 (HR: 1.74, 95% CI: 1.04–2.90; $p = 0.034$), use of nephrotoxic drugs (HR: 3.12, 95% CI:1.18–8.20; $p = 0.021$), mucositis (HR:2.13, 95% CI: 1.28–3.52; $p = 0.003$), thrombotic microangiopathy, or sinusoidal obstructive syndrome ((HR: 2.52, 95% CI: 1.41–4.50; $p = 0.002$), shock (HR: 4.11, 95% CI: 2.28–7.45; $p = < 0.001$) (Table 2).

In the multivariable analysis, variables independently associated with a higher incidence of AKI included: nephrotoxic drugs (HR: 2.87, 95%CI:1.07–7.65; $p = 0.035$), mucositis (HR:1.95, 95% CI:1.16–3.29; $p = 0.012$), and shock (HR: 2.63, 95% CI:1.19–5.85; $p = 0.017$) (Table 3).

AKI prognostic impact

At the end of the three years after autologous HSCT, 42 (36.5%) patients had died. Fifty-two percent of deaths occurred within the first year after autologous HSCT.

In univariable analysis, the variables with impact on mortality were relapse (HR:6.24, 95%CI:2.94–13.24;

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

Patients characteristics	Category	n (%)	P50	P25	P75
Age at transplant (years)			50.2	33.9	59.5
Gender	Male	59 (51.3)			
Race	Caucasian	105 (91.3)			
BMI (kg/m²)			25.3	21.8	35.9
HCT-CI	0–1	97 (84.4)			
	≥2	18 (15.6)			
Hematologic diagnosis	B-cell lymphomas	73 (63.5)			
	Hodgkin lymphomas	37 (32.2)			
	T-cell lymphomas	5 (4.4)			
Nr of prior cycles of therapy			9	7	10
Previous radiotherapy	yes	22 (19.3)			
Basal eGFR (ml/min/1.73 m²)			107.5	94.3	124.6
Induction regimen	BEAM	109 (94.8)			
	TEAM	6 (5.2)			
Cells source	perihperal blood	111 (96.5)			
	bone marrow	4 (3.5)			
Period of aplasia (days)			10	10	11
Sepsis		26 (22.6)			
Nephrotoxic drugs		103 (89.6)			
Mucositis		74 (64.4)			
TMA/TLS/SOS		6 (5.3)			
Shock		8 (6.9)			
At hospital admission day:					
Hemoglobin (gr/dl)			11.5	10.3	12.7
Leukocytes (cells/mm³)			5620	4000	7340
Neutrophils (cells/mm³)			3530	2490	5290
Lymphocytes (cells/mm³)			1040	800	1820
Platelets (/µl)			194,000	140,000	273,000
Urea (mg/dl)			34	28	39
Uric Acid (mg/dl)			5	4.2	6
Calcium (mg/dl)			9	8.9	10
Phosphate (mg/dl)			4	3.2	4.1
Reactive C protein (mg/dl)			0.52	0.21	1
Lactate dehydrogenase (U/l)			342	297	419
Albumin (mg/dl)			4.1	3.8	4.4
Alanine transaminase (U/l)			21	15	30
Total bilirubin (mg/dl)			0.4	0.3	0.6

P50: median; P25–25th percentile: P75–75th percentile; P25 BMI: body mass index; HCT-CI: hematopoietic stem cell transplant comorbidity index; Nr: number; eGFR: estimated glomerular filtration rate; BEAM: carmustine, etoposide, cytarabine, and melphalan; TEAM: thiotepa, etoposide, cytarabine, and melphalan; TMA/TLS/SOS: thrombotic microangiopathy, tumor lysis syndrome, or sinusoidal obstruction syndrome.

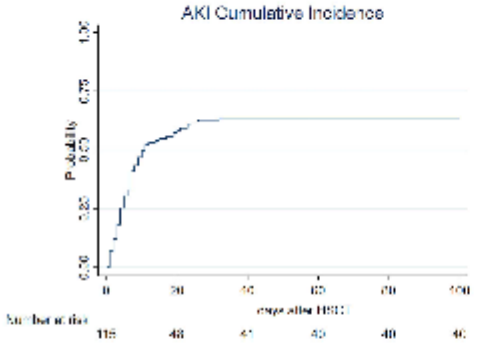

Figure 1. Cumulative incidence of AKI post HSCT. Cumulative incidence function of AKI according to the KDIGO classification using serum creatinine rise criteria and urinary output criteria. Death was considered a competing event. AKI: acute kidney injury.

$p = <0.001$) and moderate to severe AKI ((HR:2.04, 95%CI:1.06–3.94; $p = 0.033$).

In multivariable model, the variables that were independently associated with a lower overall survival were relapse (HR:5.34, 95%CI:2.55–22.30; $p = <0.001$), BMI (HR:0.91, 95%CI:0.84–0.91; $p = 0.025$) and moderate to severe AKI ((HR:2.05, 95%CI:1.10–3.82; $p = 0.024$) (Table 4).

Overall survival according to moderate-to-severe AKI is shown in Figure 2.

Cumulative incidence of relapse was 45.2% at three years after HSCT. No statistically significant association was found between AKI (nor moderate-to-severe AKI) with lower disease-free overall survival.

None of the patients had CKD previous to HSCT and their median eGFR was 107.5 (94.3–124.6) ml/min/1.73 m². One year after HSCT none of the survivors had CKD and the median eGFR was 103.7 (87.9–121.6) ml/min/1.73 m. Despite the absence of CKD, 31.2% of the survivors had an eGFR reduction superior to 25% comparing to the baseline previous to HSCT. No association was found between this reduction and previous AKI ($p = 0.730$).

Table 2. Competitive risk regression. Univariable analysis for AKI.

Patients and transplant-related characteristics	Hazard ratio estimate	95% Confidence interval		p Value
		Lower limit	Upper limit	
Age at transplant (years)	1	0.99	1.02	0.393
Gender	0.84	0.54	1.31	0.457
Race	0.94	0.38	2.35	0.903
BMI (kg/m^2)	1.03	0.99	1.08	0.185
HCT-CI $\geq$ 2	1.74	1.04	2.9	0.034
Hematologic diagnosis:				
Hodgkin lymphomas comparing B-cell lymphomas	1.1	0.67	1.81	0.69
B-cell lymphomas comparing T-cell lymphomas	1.21	0.53	2.8	0.648
Hodgkin lymphomas comparing T-cell lymphomas	1.33	0.56	3.18	0.532
Nr of prior cycles of therapy	0.98	0.91	1.05	0.647
Previous radiotherapy	1	0.57	1.77	0.977
basal eGFR (ml/min/1.73 m^2)	0.99	0.98	1	0.192
Induction regimen	0.63	0.22	1.82	0.398
Cells source	1.74	0.55	5.55	0.348
Period of aplasia (days)	0.95	0.82	1.11	0.54
Sepsis	0.8	0.5	1.26	0.347
Nephrotoxic drugs	3.12	1.18	8.2	0.021
Mucositis	2.13	1.28	3.52	0.003
TMA/SOS	2.52	1.41	4.5	0.002
Shock	4.11	2.28	7.45	<0.001
At hospital admission day:				
Hemoglobin (gr/dl)	1.01	0.87	1.16	0.908
Leukocytes (cells/mm^3)	1	1	1	0.447
Neutrophils (cells/mm^3)	1	0.99	1	0.672
Lymphocytes (cells/mm^3)	1	0.99	1	0.523
Platelets (/µl)	1	0.99	1	0.603
Urea (mg/dl)	1.01	0.99	1.01	0.172
Uric Acid (mg/dl)	1.06	0.94	1.21	0.326
Calcium (mg/dl)	0.88	0.56	1.4	0.586
Phosphate (mg/dl)	0.92	0.7	1.2	0.523
Reactive C protein (mg/dl)	0.96	0.88	1.04	0.312
Lactate dehydrogenase (U/l)	1	1	1	0.292
Albumin (mg/dl)	0.94	0.59	1.52	0.812
Alanine transaminase (U/l)	1	0.99	1.01	0.333
Total bilirubin (mg/dl)	0.92	0.76	1.14	0.481

BMI: body mass index; HCT-CI: hematopoietic stem cell transplant comorbidity index; Nr; number; eGFR: estimated glomerular filtration rate; BEAM: carmustine, etoposide, cytarabine, and melphalan; TEAM: thiotepa, etoposide, cytarabine, and melphalan; TMA/TLS/SOS: thrombotic microangiopathy, tumor lysis syndrome, or sinusoidal obstruction syndrome.

Table 3. Competitive risk regression. Multivariable analysis for AKI.

Patients and transplant-related Characteristics	Hazard ratio estimate	95% Confidence interval		p Value
		Lower limit	Upper limit	
Nephrotoxic drugs	2.87	1.08	7.65	0.035
Mucositis	1.95	1.16	3.29	0.012
MAT/TLS/SOS	2.00	0.73	5.54	0.182
Shock	2.64	1.19	5.85	0.017
Gender	0.97	0.61	1.52	0.882
BMI	1.02	0.97	1.08	0.428
HCT-CI $\geq$ 2	1.48	0.81	2.69	0.200
Age at transplant	0.99	0.97	1.01	0.378
basal eGFR	0.99	0.98	1.00	0.125
Cells source	1.71	0.66	4.44	0.273
Induction regimen	0.69	0.22	2.16	0.523

BMI: body mass index; HCT-CI: hematopoietic stem cell transplant comorbidity index; eGFR: estimated glomerular filtration rate; TMA/TLS/SOS: thrombotic microangiopathy, tumor lysis syndrome, or sinusoidal obstruction syndrome.

Three years after HSCT 2.2% of the survivors had CKD and the median eGFR was 98.6 (80.1 – 115.8) ml/min/1.73 m. An eGFR reduction superior to 25% was registered in 31.8% of the survivors when comparing to the baseline eGFR previous to HSCT and 10% when comparing to eGFR 1 year after HSCT. No association was found between this reduction and previous AKI ($p = 0.113$).

Table 4. Cox proportional hazards model regression. Multivariable analysis for mortality.

Patients and transplant-related characteristics	Hazard ratio estimate	Standard error	95% Confidence interval		p Value
			Lower limit	Upper limit	
Relapse	6.24	2.39	2.94	13.23	<0.001
Moderate to severe AKI	2.04	0.68	1.06	3.94	0.033
Age at transplant	1.02	0.01	0.99	1.04	0.18
Race	3.42	3.69	0.41	28.52	0.256
BMI	0.91	0.04	0.84	0.99	0.025
HCT-CI ≥ 2	2.08	0.88	0.91	4.76	0.083

AKI: acute kidney injury; BMI: body mass index; HCT-CI: hematopoietic stem cell transplant comorbidity index.

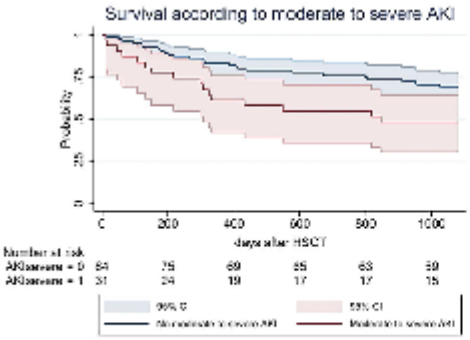

Figure 2. Overall survival considering moderate-to-severe AKI. Overall survival in days in the first 3 years of HSCT considering moderate to severe AKI according to the KDIGO classification using serum creatinine rise criteria and urinary output criteria. AKI: acute kidney injury; CI: confidence interval; HSCT: hematopoietic stem cell transplant.

Discussion

In our study we found a cumulative incidence of AKI and moderate-to-severe AKI of 63.7% and 27.1%, respectively, using KDIGO classification and both creatinine and urinary output criteria.

A meta-analysis published in 2020 by Kanduri et al. considering 5144 patients submitted to either allogeneic or autologous HSCT presented an incidence of AKI and severe AKI of 55.1% and 8.3% [15]. Considering autologous HSCT studies, data by Lopes et al. show an AKI incidence of 12% [16], Fadia et al. found an AKI incidence of 21% [17], Caliskan et al. found and AKI incidence of 52% [18] and, similarly, Merouani et al. report an AKI incidence of 56% [19]. These previous studies used different AKI definitions and did not take in consideration urinary output criteria. Our higher incidence compared to other studies on autologous HSCT may be explained by a more updated and complete AKI definition (KDIGO classification including both creatinine and urinary output criteria) which we believe to contribute to more accurate results.

One aspect we consider worth notice in our study is that although moderate-to-severe AKI represented 19.2% of AKI cases on AKI day of onset, this severity represented 41.5% when considering the highest stage reached. These grades of severity were independently associated with lower overall survival. An earlier approach in less severe AKI stages may reduce the probability of progression to more severe stages and improve outcomes. In our study, urinary output reduction alone was the first criteria to be present on the day of AKI onset in more than forty percent of AKI patients. Thus, urinary output monitorization is of major importance in these patients and should be taken in account in clinical practice to approach AKI as soon as possible to prevent progression of AKI.

Known risk factors and causes for AKI in the general population - namely nephrotoxic drugs and episode of shock – had an expected significantly higher incidence in patients with AKI in our lymphoma patients submitted to autologous HSCT. This result has been consistently suggested in other studies [19–23]. Focusing on other risk factors and causes of AKI specific of HSCT, mucositis showed a strong statistically significant association with AKI, which was also found by Andronesi et al. in his study on autologous HSCT in multiple myeloma patients [24].

Our study did not find an association between lower baseline eGFR with AKI as other autologous HSCT studies did. We believe this is related to the fact that our patients did not have CKD (eGFR was 107.5 ml/min/1.73 m^2 (94.3–124.6 IQR), as patients with lymphoma tend to be much younger and previously healthier than patients with multiple myeloma or amyloidosis (included in other autologous HSCT studies).

AKI is a risk factor for lower short- and long-term overall survival in different scenarios and populations, and there is a graded relationship between severity of AKI and increased mortality [25–28]. Although our results on overall survival with a 3-year follow up period in patients with lymphoma submitted to autologous HSCT had no significant association with AKI, moderate-

to-severe AKI showed an independent association with lower overall survival (HR:2.05, 95%CI:1.10–3.82; $p = 0.024$). Andronesi et al. also did not find higher mortality rates in autologous HSCT with AKI including all stages [24] and studies considering HSCT in general have demonstrated that mortality rates increase as the severity of AKI increases [29–31]. Our results enlighten this finding in autologous HSCT in lymphoma patients and reinforce the need for monitoring and an early approach to AKI in these patients to prevent progression to higher AKI stages ultimately associated with worse prognosis.

Our population did not have CKD previous to the HSCT. We registered a reduction of eGFR > 25% in around one quarter of the patients but only 2.2% of patients progressed to CKD 3 years after HSCT. These renal outcomes were not significantly associated to previous AKI although Gutierrez et al. [32] and Sakaguchi et al. [33] found an association between AKI and progression to CKD in HSCT. These authors focused on allogeneic HSCT in patients with leukemia and multiple myeloma. Allogeneic HSCT includes aggressive induction chemotherapy as well as calcineurin inhibitors chronically administered after the HSCT and patients have different outcomes related to their baseline disease. Also, these studies included patients with CKD prior to HSCT which is a known risk factor and had longer follow-up periods. Still, we believe that we would need higher number of patients considering the high mortality rate of our population and longer period of follow up to infer long-term impact on renal outcomes.

As a single-center retrospective study, we acknowledge limitations related to external validity and data availability. Patients had often two or more nephrotoxic drugs previous to AKI which does not allow to extract information on which nephrotoxic had higher impact on AKI. Also, other criteria for CKD like proteinuria or structural abnormalities were not available as well as other serum creatinine measures between 1 year and 3 years after HSCT.

Despite these limitations, to the best of our knowledge, this is the first study focusing exclusively on this hematological malignancy group submitted to autologous HSCT using KDIGO classification. It is also the first study to consider not only creatinine criteria but also UO criteria to diagnose and categorize AKI in an HSCT population.

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

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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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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.

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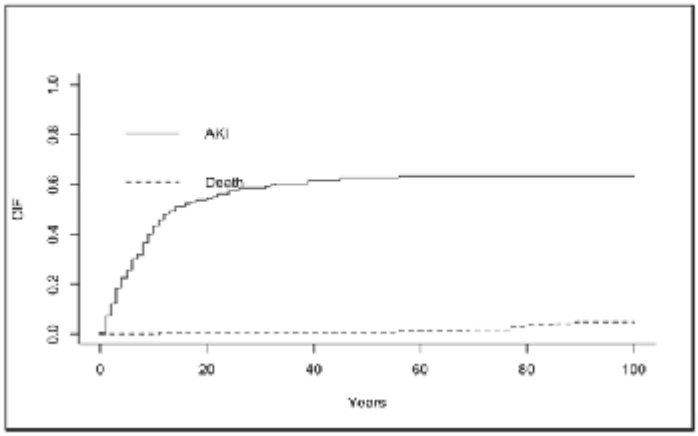
Table 1: Patients' baseline characteristics and transplant related variables.

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

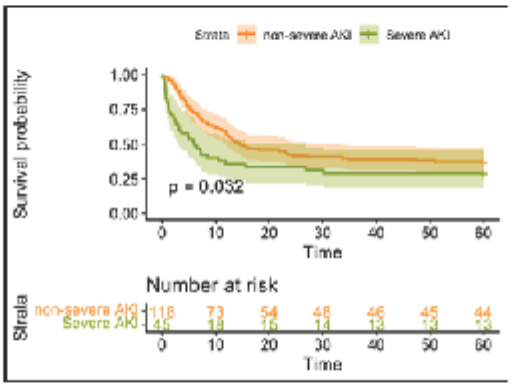


Figure 2: Overall survival in months according to severe AKI.

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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Article

Predictive Risk Score for Acute Kidney Injury in Hematopoietic Stem Cell Transplant

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Simple Summary: The incidence and prevalence of hematologic malignancies are increasing throughout the world and hematopoietic stem cell transplant contributes to significantly better outcomes. Acute kidney injury is a frequent complication of hematopoietic stem cell transplants and has known implications for overall survival. We calculated the first simple, easily assessed, inexpensive predictive risk score that helps identify patients with hematologic malignancies undergoing a hematopoietic stem cell transplant at risk for AKI.

Abstract: Hematopoietic stem cell transplant (HSCT) is an important treatment option for hematologic malignancies. Acute kidney injury (AKI) is a common complication in HSCTs and is related to worse outcomes. We aimed to create a predictive risk score for AKI in HSCT considering variables available at the time of the transplant. We performed a retrospective cohort study. AKI was defined by the KDIGO classification using creatinine and urinary output criteria. We used survival analysis with competing events. Continuous variables were dichotomized according to the Liu index. A multivariable analysis was performed with a backward stepwise regression. Harrel's C-Statistic was used to evaluate the performance of the model. Points were attributed considering the nearest integer of two times each covariate's hazard ratio. The Liu index was used to establish the optimal cut-off. We included 422 patients undergoing autologous (61.1%) or allogeneic (38.9%) HSCTs for multiple myeloma (33.9%), lymphoma (27.3%), and leukemia (38.8%). AKI cumulative incidence was 59.1%. Variables eligible for the final score were: hematopoietic cell transplant comorbidity index ≥2 (HR: 1.47, 95% CI: 1.08–2.006; $p = 0.013$), chronic kidney disease (HR: 2.10, 95% CI: 1.31–3.36; $p = 0.002$), lymphoma or leukemia (HR: 1.69, 95% CI: 1.26–2.25; $p < 0.001$) and platelet-to-lymphocyte ratio > 171.9 (HR: 1.43, 95% CI: 1.10–1.86; $p = 0.008$). This is the first predictive risk score for AKI in patients undergoing HSCTs and the first study where the platelet-to-lymphocyte ratio is independently associated with AKI.

Keywords: stem cell transplant; risk factors; predictive risk score

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1. Introduction

The incidence and prevalence of hematologic malignancies are increasing throughout the world [1,2]. Several factors contribute to this evidence. Diagnostic standardization according to universal classification systems such as the World Health Organization Classification of Tumour and Haematopoietic and Lymphoid Tissues [3] has resulted in better data collection and higher reporting on regional and international cancer registries. Also, earlier and more precise diagnoses have been a predictable consequence of the evolution

of cancer genetic and molecular testing technologies. These two factors have partially overcome underdiagnosis and under-reporting, contributing to a higher incidence of hematologic malignancies. Advanced age is a well-recognized risk factor for cancer development and is partially related to DNA damage accumulation and immunosenescence [4]. The aging of the global population has resulted in a steady increase in hematologic malignancies, both lymphoid and myeloid neoplasms [5]. Higher cancer survivorship rates due to improvements in oncology care have paradoxically created conditions for the development of therapy-related secondary myeloid malignancies [6], which tend to occur in long-term survivors.

With the increasing prevalence of hematologic malignancies, the overall number of patients requiring HSCTs has also evolved. HSCT is a potentially curative treatment for virtually all hematologic cancers and the therapeutic benefits result from high-dose chemotherapy and the graft vs. tumor effect that develops after allografting. Acute leukemias are the most common indications for allogeneic HSCTs [7]. Leukemias harboring adverse genetic events are at high risk of relapse after intensive chemotherapy, and post-remission allografting is the only available treatment modality that can result in a cure or long-term survival [7]. Multiple myeloma is the most common adult indication for autologous HSCTs [7]. The steep dose–response curve for high-dose melphalan in patients with myeloma results in meaningful clinical benefits after HSCT and this treatment modality delays progression and improves median overall survival by approximately 12 months [8]. Relapsed/refractory Hodgkin (HL) and non-Hodgkin lymphomas (NHL) are the second most common adult indications for autologous HSCTs [7] and curability rates are high. The fact that increasing alkylating agent dosing can overcome the resistance of most lymphoma cells defines the biological rationale for the clinical use of autologous HSCT in second-line HL and NHL. In relapsed/refractory diffuse large B cell lymphoma, the most common NHL, the role of HSCTs has been prospectively established and compared to chemotherapy alone; 5-year event-free survival and overall survival were significantly superior in the transplant arm (46% and 53% vs. 12 and 32%, respectively) [9]. In HL, a disease of young adults, autologous HSCT is the standard of care in the relapsed/refractory setting and results in a cure rate of 50% [10].

The number of HSCTs performed has increased 7% per year worldwide from 10,000 HSCTs per year in 1991 to 82,718 first HSCTs per year in 2016, with slightly more autologous (53.5%) than allogeneic HSCTs. HSCT activity has been reported from 87 of the 195 World Health Organization (WHO) member states [11]. More than ever, a better characterization of short- and long-term complications of HSCTs is needed.

Acute kidney injury (AKI) is a possible complication of an HSCT and is known to occur predominantly in the first 100 days after this procedure [12]. The most recent definition of AKI—the Kidney Disease Improving Global Outcome (KDIGO) classification [13]—has been responsible for the uniformization of the various previous definitions in clinical practice, research and public health, contributing to more accurate studies on this matter.

In the last five years, studies have been published on AKI in HSCTs showing an incidence above fifty percent in most studies and a consistent prognostic impact on overall survival, especially in the higher stages of AKI [12,14–18].

AKI still does not have a specific treatment besides treating the cause, which is not always easily identifiable. Prevention and early approach are the best recommendable clinical attitudes [13]. We do consider a predictive risk score for AKI—that can be calculated at hospital admission before undergoing an HSCT for any haemato-oncological diagnosis—to be very useful for the management of these patients.

Our study aims to (1) determine the incidence of AKI in patients undergoing HSCTs using the KDIGO classification with both creatinine and urinary output criteria; (2) to identify independent risk factors for AKI that can be available to the clinician before undergoing an HSCT; and (3) to create a predictive risk score for AKI.

Appendix C

2. Materials and Methods

2.1. Study Design, Population, and Data Collection

This study was performed considering a single-center retrospective cohort of patients undergoing HSCTs at a tertiary hospital between January 2005 and December 2015. We excluded patients with a previous HSCT, patients with chronic kidney disease already on renal replacement therapy, patients who underwent renal replacement therapy one week before transplantation and patients under the age of 18 years.

The conditioning regimens used followed institutional protocols and none of the patients underwent previous total body irradiation because it is not available at our institution.

Data collection was based on registers of appointments for HSCT eligibility, on registers of the hospital admission period for HSCT (including six-hour period nurses' records of urinary output and all laboratory analyses performed during this period) and all appointments and hospital admissions in the first 100 days after HSCT.

The following variables were collected: patient's demographic characteristics (age, gender, race, body weight and height), patient's comorbidities (diabetes mellitus, hypertension, chronic kidney disease, arrhythmia, valvular heart disease, ischemic heart disease, cerebrovascular disease, chronic liver disease, intestinal inflammatory disease, peptic ulcer, connective tissue disease, chronic obstructive pulmonary disease, solid-organ cancer, psychiatric disease), hematological diagnosis (type of hematological malignancy), transplant´s characteristics (type of transplant, type of donor, cells' source, induction regimen), laboratory blood panel at admission day (complete hemogram, albumin, uric acid, calcium, phosphate, bilirubin, lactate dehydrogenase, alanine transaminase) and AKI or death during the first 100 days.

2.2. Definitions

Chronic kidney disease (CKD) was defined as a persistent decrease in estimated glomerular filtration rate to below 60 mL/min/1.73 m^2, according to the definition of KDIGO [19].

The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) [20] was calculated according to the latest validated version considering patients' comorbidities.

Body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the square of their height in meters.

Platelet-to-lymphocyte ratio was calculated by dividing platelet count by lymphocyte count.

Baseline glomerular filtration rate was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21], considering serum creatinine at the last medical appointment before hospital admission for HSCT as baseline serum creatinine.

AKI diagnosis was made based on daily values of serum creatinine and 6 h urinary output until hospital discharge and all other hospital admissions or weekly evaluations at an outpatient clinic for the first 100 days after undergoing HSCT. AKI was defined by the KDIGO criteria [5] (any of the following: increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h; increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urinary output <0.5 mL/kg/h for 6 h).

2.3. Statistical Methods

Categorical variables were described as frequencies, continuous variables with normal distribution were expressed as mean and standard deviation (SD), and other continuous variables were expressed as median and interquartile range (P25 = 25th percentile; P75 = 75th percentile).

We followed the statistical methodology suggested by the European Group for Blood and Marrow Transplantation [22]. We used survival analysis methods considering competing events—we considered death a competing risk event—through the Fine and Gray method [23] to calculate the cumulative incidence of AKI and perform univariable and

multivariable analyses of factors predicting AKI. To establish the multivariable model for the creation of the clinical score, continuous variables that presented a $p < 0.2$ were dichotomized according to the Liu index. The resulting categorical variables were tested for their association with the risk of incident AKI, and a multivariable analysis was performed with a backward stepwise regression (entry criteria—$p < 0.2$). Harrel's C-Statistic was used to evaluate the performance of the model, and a risk score was created by attributing points corresponding to the nearest integer of two times each covariate's hazard ratio. The Liu index was used further to establish the optimal cut-off for the clinical risk score, and a log-rank test and respective reverse Kaplan–Meier curves were used to compare the event distributions of the resulting score categorical variable.

Missing data for all variables represented less than 10%; therefore, no imputation techniques were used. Analyses were performed with the statistical software package STATA 16.0 for Windows.

3. Results

Five hundred and thirty-four patients underwent HSCT at our center between January 2005 and December 2015. Among these patients, one hundred and twelve patients were excluded for presenting at least one exclusion criteria and 422 patients were eligible for the study.

Patients' baseline characteristics and transplant-related aspects are shown in Table 1.

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

Patients Characteristics	Category	n (%)	P50	P25	P75
Age at transplant (years)			50.2	36.0	59.5
Gender	Male	236 (55.9)			
	Female	186 (44.1)			
Race	Caucasian	385 (91.4)			
	Non-Caucasian	37 (8.6)			
BMI (Kg/m^2)			24.6	21.9	27.8
HCT-CI	0–1	353 (84.3)			
	≥2	66 (15.8)			
Hypertension		88 (20.9)			
Diabetes mellitus		26 (6.2)			
Congestive heart failure		23 (5.5)			
Chronic kidney disease		27 (6.4)			
Hematologic diagnosis	Leukaemia	164 (38.8)			
	Lymphoma	115 (27.3)			
	Multiple myeloma	143 (33.9)			
Type of HSCT	Autologous	258 (61.1)			
	Allogeneic	164 (38.9)			
Type of donor	Self	258 (61.1)			
	Related	92 (21.8)			
	Not related	72 (17.1)			
Previous radiotherapy	yes	82 (19.5)			
basal eGFR (ml/min/1.73 m^2)			107.3	94.3	122.1
Conditioning regimen	Myeloablative	305 (72.2)			
	Non-myeloablative	117 (27.8)			
Graft source	Peripheral blood	389 (92.2)			
	Bone marrow	33 (7.8)			
GVHD prophylaxis	CsA + MMF	117 (27.7)			
	CsA + MTX	47 (11.1)			
	None	258 (61.1)			
At hospital admission day:					
Hemoglobin (gr/dL)			11.6	10.2	12.6
Leukocytes (cells/mm^3)			4920	3500	6860
Neutrophils (cells/mm^3)			2960	1850	4420

Table 1. *Cont.*

Patients Characteristics	Category	n (%)	P50	P25	P75
Platelets (/µL)			179,000	127,000	245,000
Urea (mg/dL)			33	27	41
Uric acid (mg/dL)			5	4	6
Calcium (mg/dL)			9	8.8	10
Phosphate (mg/dL)			4	3.2	4.1
Reactive C protein (mg/dL)			0.49	0.15	2
Lactate dehydrogenase (U/L)			339	291	426
Albumin (mg/dL)			4	3.7	4.5
Alanine transaminase (U/L)			22	15	37
Total bilirubin (mg/dL)			0.48	0.36	0.61
Platelet-to-lymphocyte ratio			159.9	94.1	265.4

SD—standard deviation; P50—median; P25—25th percentile; P75—75th percentile; P25 BMI—body mass index; HCT-CI—hematopoietic stem cell transplant comorbidity index; eGFR—estimated glomerular filtration rate; CsA—cyclosporine; MMF—mycophenolate mofetil; MTX—methotrexate.

3.1. AKI—Cumulative Incidence

The AKI cumulative incidence was 59.1% at 100 days after HSCT (Figure 1).

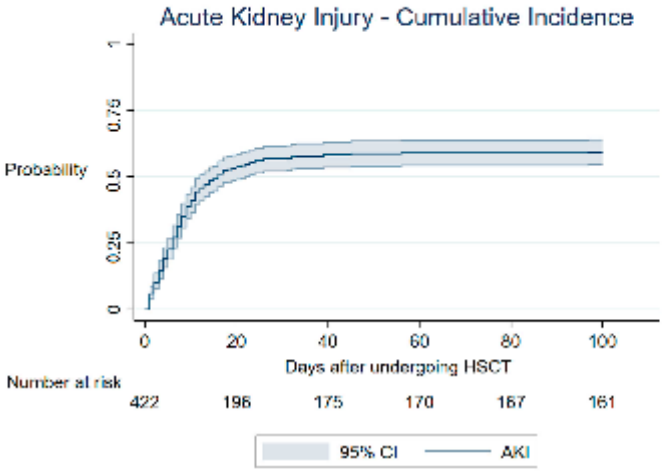


Figure 1. Cumulative incidence of AKI post-HSCT. Cumulative incidence function of AKI according to the KDIGO classification using serum creatinine rise criteria and urinary output criteria. Death was considered a competing event. HSCT—hematopoietic stem cell transplant; CI—cumulative incidence; AKI—acute kidney injury.

3.2. Variable Analysis and Predictive Score for AKI

In the univariable analysis performed for AKI, considering death as a competing event, the variables associated with AKI in this analysis were HCT-CI $\geq$ 2, chronic kidney disease, hematologic diagnosis—leukemia or lymphoma, basal eGFR, leukocytes count at admission, lymphocytes count at admission, reactive C protein at admission, lactate dehydrogenase at admission and platelet-to-lymphocyte ratio at admission. Each variable with its respective hazard ratio, confidence interval and *p*-value is shown in Table 2.

Table 2. Univariable analysis for AKI including all variables.

Patient's Characteristics	HR Estimate	95% CI		*p*-Value
		Lower Limit	Upper Limit	
Age at transplant (years)	1.00	0.99	1.01	0.830
Gender (female versus male)	1.05	0.83	1.35	0.654
Race (Caucasian versus non-Caucasian)	0.90	0.58	1.40	0.634
BMI (Kg/m^2)	1.02	1.00	1.05	0.105
HCT-CI (score < 2 versus score ≥ 2)	1.69	1.27	2.25	<0.001
Hypertension	1.15	0.86	1.54	0.335
Diabetes mellitus	1.29	0.82	2.02	0.269
Congestive heart failure	1.41	0.91	2.20	0.128
Chronic kidney disease	2.11	1.36	3.27	0.001
Hematologic diagnosis:				
Multiple myeloma versus lymphoma	1.51	1.10	2.08	0.011
Multiple myeloma versus leukemia	1.44	1.07	1.92	0.015
Leukemia versus lymphoma	1.05	0.78	1.41	0.728
Multiple myeloma versus (lymphoma + leukemia)	1.46	1.12	1.90	0.005
Type of HSCT (allogeneic versus autologous)	0.84	0.66	1.08	0.169
Type of donor (related versus unrelated)	1.14	0.86	1.52	0.368
Previous radiotherapy	1.09	0.81	1.47	0.573
Conditioning regimen (non-myeloablative versus myeloablative)	1.27	0.84	1.95	0.260
basal eGFR (ml/min/1.73 m^2)	0.99	0.99	1.00	0.012
Graft source (peripheral blood versus bone marrow)	1.36	0.88	2.12	0.170
GVHD prophylaxis (methotrexate versus others)	1.03	0.73	1.46	0.849
At hospital admission day:				
Hemoglobin (gr/dL)	1.01	0.94	1.09	0.752
Leukocytes * (cells/mm^3)	1.07	1.04	1.09	<0.001
Neutrophils * (cells/mm^3)	1.06	0.88	1.26	0.547
Lymphocytes * (cells/mm^3)	1.23	1.13	1.34	<0.001
Platelets * (/μL)	1.01	0.99	1.02	0.841
Urea (mg/dL)	1.01	1.00	1.02	0.019
Uric acid (mg/dL)	1.01	0.97	1.04	0.662
Calcium (mg/dL)	1.06	0.85	1.31	0.598
Phosphate (mg/dL)	0.92	0.77	1.10	0.367
Reactive C protein ** (mg/dL)	1.02	1.01	1.03	<0.001
Lactate dehydrogenase ** (U/L)	1.05	1.03	1.07	<0.001
Albumin (mg/dL)	1.00	0.96	1.04	0.847
Alanine transaminase (U/L)	1.00	0.99	1.00	0.081
Total bilirubin (mg/dL)	0.91	0.62	1.32	0.611
Platelet-to-lymphocyte ratio	1.00	1.00	1.00	<0.001

*—for each rise of 1000; **—for each rise of 10; BMI—body mass index; HCT-CI—hematopoietic stem cell transplant comorbidity index; Nr—number; HSCT—hematopoietic stem cell transplant; eGFR—estimated glomerular filtration rate; GVHD—grafts versus host disease.

Considering only variables of Table 2 with $p < 0.200$ and applying the Liu index to establish the optimal cut-off point for each variable, the variables associated with AKI in the univariable analysis were HCT-CI ≥ 2, chronic kidney disease and hematologic diagnosis—leukemia or lymphoma. Each variable with its respective hazard ratio, confidence interval and *p*-value are presented in Table 3.

Appendix C

Table 3. Univariable analysis for AKI including the selected variables ($p < 0.200$ in Table 2) after applying the Liu index and establishing the optimal cut-off point.

Patient's Characteristics	HR Estimate	95% CI		*p*-Value
		Lower Limit	Upper Limit	
BMI (>24.5 Kg/m^2)	1.20	0.94	1.53	0.147
HCT-CI (socre < 2 versus score ≥ 2)	1.69	1.27	2.25	<0.001
Congestive heart failure	1.41	0.91	2.2	0.128
Chronic kidney disease	2.11	1.36	3.27	0.001
Hematologic diagnosis (multiple myeloma versus (lymphoma + leukemia)	1.46	1.12	1.91	0.005
Type of HSCT (allogeneic versus autologous)	0.84	0.66	1.08	0.169
basal eGFR (>107.2 mL/min/1.73 m^2)	0.89	0.7	1.13	0.342
Graft source (peripheral blood versus bone marrow)	1.36	0.88	2.12	0.170
Leukocytes (>5330 cells/mm^3)	1.05	0.82	1.34	0.696
Lymphocytes (>1100 cells/mm^3)	0.89	0.7	1.13	0.334
Urea (>30 mg/dL)	1.15	0.9	1.48	0.263
Reactive C protein (>0.47 mg/dL)	1.20	0.92	1.55	0.176
Lactate dehydrogenase (>339 U/L)	1.26	0.98	1.61	0.066
Alanine transaminase (>22 U/L)	1.02	0.8	1.31	0.853
Platelet-to-lymphocyte ratio (>171.9)	1.26	0.97	1.62	0.078

BMI—body mass index; HCT-CI—hematopoietic stem cell transplant comorbidity index; HSCT—hematopoietic stem cell transplant; eGFR—estimated glomerular filtration rate.

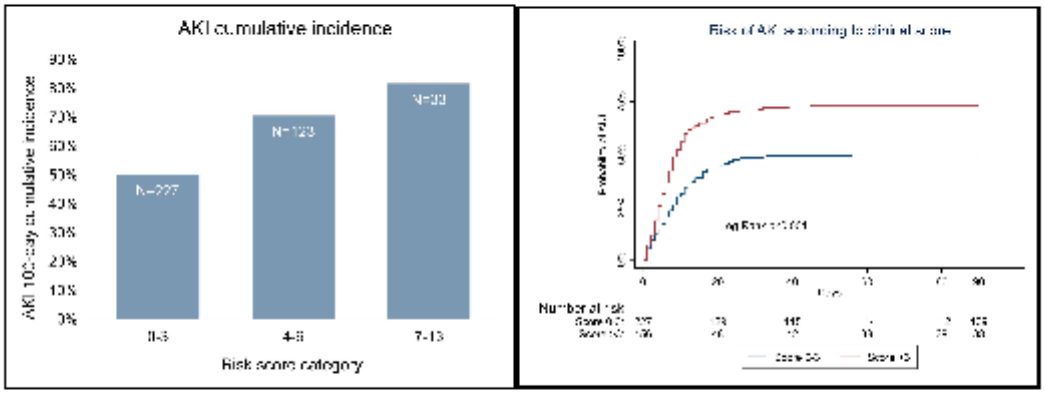
In multivariable analysis, the variables with independent association with AKI were HCT-CI ≥ 2 (HR: 1.47; 95% CI: 1.08–2.00; $p = 0.013$), chronic kidney disease (HR: 2.10; 95% CI: 1.31–3.36; $p = 0.002$), hematologic diagnosis—leukemia or lymphoma (HR: 1.69; 95% CI: 1.26–2.25; $p < 0.001$) and platelet-to-lymphocyte ratio > 171.9 (HR: 1.43; 95% CI: 1.10–1.86; $p = 0.008$) (Table 4).

Table 4. Multivariable analysis for AKI with Score points.

Patient's Characteristics	HR Estimate	95% CI		*p*-Value	Score Points
		Lower Limit	Upper Limit		
HCT-CI (reference category < 2)	1.47	1.08	2.00	0.013	3
Chronic kidney disease	2.10	1.31	3.36	0.002	4
Hematologic diagnosis (reference category multiple myeloma)	1.69	1.26	2.25	<0.001	3
Platelet-to-lymphocyte ratio (reference category < 171.9)	1.43	1.1	1.86	0.008	3
Multivariable model C-Statistic = 0.71					
Score C-Statistic = 0.70					

HCT-CI—hematopoietic stem cell transplant comorbidity index.

The attributable score points to each variable are shown in Table 4. AKI cumulative distribution by score is shown in Figure 2. For a score >3, there was a higher unadjusted risk of incident AKI at 100 days of follow-up (log-rank < 0.001), with an AKI probability of 75.6% [95% CI 82–68.7%] (N day 0 = 227, N day 100 = 107), while patients with a score of 0–3 presented a probability of 47.2% [40.5–53.5%] (N day 0 = 156, N day 100 = 38).



(A) (B)

Figure 2. (**A**) AKI cumulative incidence at 100 days according to different score categories. (**B**) AKI distribution curves by score category (score 0–3 and score >3).

4. Discussion

The wide range of AKI incidence in HSCTs amongst older studies—from 20% to 92% [24]—has been explained in part by the use of different AKI definitions. The most recent definition of AKI, the KDIGO classification [13], was proposed in 2012. It resulted from the fusion of the former classifications Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) [25] in 2004 and the Acute Kidney Injury Network (AKIN) [26] and has been used worldwide aiming the uniformization of this concept in the scientific community.

In our study, 59.1% of patients undergoing HSCTs developed AKI as defined by the KDIGO classification considering both creatinine and urinary output criteria in the first 100 days after HSCT. This cumulative incidence is in the range of recent studies (49.2–68.9%) that consider KDIGO classification—either by creatinine criteria alone [12,14,18] or by both creatinine and urinary output criteria [15,16] in populations with different hematologic malignancies undergoing HSCTs.

These same studies consistently associated AKI in the first 100 days after HSCT with lower overall survival—Kanduri et al. (2020) published a meta-analysis [13] showing 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. Also, Gutierrez et al. [14] and Andronesi et al. [18] found an association between AKI in allogeneic HSCTs and progression to CKD in HSCTs. These findings reinforce the importance of identifying patients at risk to implement prevention measures and early approach.

Although many AKI risk factors occurring in the first days after HSCT have been previously identified—such as exposure to nephrotoxic drugs, moderate-to-severe mucositis, shock, sepsis graft versus host disease, veno-occlusive disease [17]—we did not include any variables that would occur after HSCTs in our model. By doing so, we assured a predictive risk score applicable at the beginning of the hospital stay that does not need to be repeated nor updated during the following days.

Our predictive risk score takes into consideration the presence of chronic kidney disease previous to HSCT, the HCT-CI score, the platelet-to-lymphocyte ratio at admission and the hematologic malignancy diagnosis. All these variables used as risk factors for the prediction of AKI are consistent with the previous literature on AKI risk factors for AKI in general.

Chronic kidney disease is an extensively known risk factor for AKI [27–29]. Chronic kidney disease results in a state of constant relative hypoxia with reduced numbers of peritubular capillaries, increased deposition of collagen, myofibroblast proliferation, increased activation of the renin–angiotensin system and reduced numbers of glomeruli, leading to hyperfiltration and higher tubular oxygen consumption of the corresponding tubules [30]. These aspects combined with the chronic leukocyte infiltration and pro-inflammatory environment of chronic kidney disease result in reduced renal reserve and maladaptation, loss of autoregulation and abnormal vasodilation, which represent the perfect conditions for enhanced susceptibility to developing AKI.

The independent association of an HCT-CI score higher than two points and AKI underscores the importance of previous comorbidities in the context of AKI. This comorbidity index takes into consideration the previous history of cardiovascular, pneumological, gastrointestinal, nephrological, rheumatological, oncological and psychiatric complications. Many of these conditions have been associated with AKI in different clinical scenarios. HCT-CI provides information about the overall, as well as non-relapse, mortality risk a patient is likely to experience after hematopoietic cell transplantation. Its application as a predictor for AKI is thus facilitated for its already worldwide use.

Platelet-to-lymphocyte ratio is a novel inflammatory marker revealing shifts in platelet and lymphocyte counts due to acute inflammatory and prothrombotic states, which has been used in several clinical contexts for predicting inflammation and mortality. It is calculated by dividing platelet count by lymphocyte count, which makes it a simple, inexpensive and rapid marker. It has been associated with worse overall survival in various solid tumors [31], with higher mortality in patients with acute heart failure [32], in septic patients [33], and in patients with rheumatic diseases [34]. It has also been reported an association between platelet-to-lymphocyte ratio and worse prognosis of septic AKI patients [35].

In our study, patients with multiple myeloma had a lower risk of developing AKI compared to patients with either lymphoma or leukemia. We believe this aspect may be related to lower treatment burden previous to HSCTs in patients with multiple myeloma, where HSCT is part of first-line treatment. Patients with lymphoma or leukemia were often exposed to high-dose chemotherapy regimens that are related to higher nephrotoxicity and the performance of HSCTs is often used when the disease relapses or progresses despite chemotherapy regimens. In contrast to myeloma, patients with lymphoma or leukemia were often exposed to high-dose chemotherapy regimens and transplanted in a relapsed/refractory setting, which contributed to nephrotoxicity. The authors consider this observation clinically valuable since myeloma patients are usually considered to be a high-risk population for AKI compared to other hematologic malignancies. However, this may not necessarily be the case during hospitalization for an autograft—a setting where at least a partial response to pre-transplant therapy is mandatory.

The main limitation of our study relates to its single-center retrospective nature and consequent limitation in the generalization of our results. Similarly, the score was developed and tested in the same group of patients, which might have overestimated its overall performance. It is expected that its C-statistic should be different in other clinical cohorts. Despite its limitation, we believe important strengths should be enlightened. Unlike most studies on AKI in HSCTs (and on AKI in general), we used both creatinine and urinary output criteria for the KDIGO classification. This aspect contributes to a more accurate diagnosis of AKI and consequently higher precision and internal validity of our results. The fact that we only used variables available at the time of hospital admission allows the score to be calculated at a single point in time and before undergoing the HSCT, which makes it more user friendly. The inclusion of patients undergoing both autologous and allogeneic HSCTs allows the application of this predictive risk score to a wider HSCT population. Also, our score was created based on clinical characteristics and laboratory results that are easily assessed, inexpensive and are currently part of the evaluation of every patient

eligible for an HSCT in all countries that offer this procedure. This aspect makes this score accessible to all clinicians at no additional cost.

Our study provides novelty in two aspects: (1) by being, to the best of our knowledge, the first study proposing a predictive risk score for AKI in patients undergoing HSCTs considering variables available at the time of hospital admission; (2) by being the first study to establish platelet-to-lymphocyte ratio as a risk factor for AKI. This score deserves further validation in multi-center prospective studies.

We believe the introduction of this kind of tool in clinical practice is crucial, as it allows the implementation of preventive measures and earlier diagnosis in patients with a higher risk of developing a complication known to have the worst prognostic impact on overall survival in this population.

5. Conclusions

In our study including 433 patients, AKI as defined by the KDIGO classification using both creatinine and urinary output criteria affected more than half of the patients undergoing HSCTs considering the first 100 days after the procedure. Considering data available before undergoing an HSCT, this complication is known to be related to lower overall survival and was associated with patients who already had chronic kidney disease, patients who presented two or more points in the HCT-CI score, patients with the underlying diagnosis of lymphoma or leukemia and patients with a platelet-to-lymphocyte ratio at hospital admission ≥171.9. Considering these findings, we developed a new calculated risk score to predict AKI in patients with hematologic malignancies undergoing an HSCT, which combines clinical and laboratorial markers available at the time of the procedure that are easily assessed and inexpensive. The development of predictive risk scores is very important—identifying patients at high risk is an essential step towards selecting those who might benefit from specific prevention measures and confers higher awareness for an earlier diagnosis.

This score should be validated with multi-center prospective studies.

Author Contributions: N.R. designed the study, collected data, analyzed data, and wrote the manuscript. M.F.-M. designed the study, analyzed data, and revised the manuscript. C.C., C.B., F.M. and P.V. collected data. C.M. revised the manuscript. A.L.-M. revised the manuscript. J.A.L. designed the study and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the local Ethical Committee—Comissão de Ética do Centro Académico de Medicina de Lisboa on the 13th of October of 2020 (reference number 334/20) in agreement with institutional guidelines. Informed consent was waived by the Ethical Committee due to the retrospective and non-interventional nature of the study. The ethical committee of Centro Académico de Medicina de Lisboa approved this study (approval number 35338) according to institutional guidelines and waived the requirement to obtain any informed consent due to its retrospective and non-interventional nature.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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Acute Kidney Injury in Multiple Myeloma patients undergoing Autologous Hematopoietic Stem Cell Transplant . Cohort study.

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Abstract:	Background Autologous hematopoietic stem cell transplant (HSCT) plays an important role in multiple myeloma (MM) treatment. Increasing incidence of MM and growing awareness of acute kidney injury (AKI) as a complication of HSCT results in the need to better understand AKI in these patients. We aimed to evaluate incidence, risk factors and 5-year prognostic impact of AKI in MM patients undergoing autologous HSCT. Methods Retrospective cohort study. AKI was defined by the KDIGO classification using creatinine and urinary output criteria. We used survival analysis methods considering competing events for risk factors and disease-free survival, Cox proportional regression for overall survival and stepwise regression methods for multivariable models. Results We analyzed 143 patients. AKI cumulative incidence was 49.7% , respectively. Factors with independent impact on AKI were BMI (HR:1.08;95%CI:1.02-1.13), HCT-CI score≥2 (HR:1.85, 95%CI:1.08-3.17), chronic kidney disease (CKD) (HR:2.06, 95%CI:1.05-4.04), amyloidosis (HR:2.25, 95%CI:1.25-4.06), moderate-to-severe mucositis (HR:2.19, 95%CI:1.25-3.86) and nephrotoxic drugs (HR:2.0856, 95%CI:1.04-4.19). Moderate-to-severe AKI had an impact (HR:1.62, 95% CI:1.15-2.31) on lower 5-year overall survival. No significant impact of AKI was found in lower disease-free overall survival nor in CKD. Conclusion AKI is frequent in MM patients undergoing autologous HSCT. Higher BMI, HCT-CI score ≥2, CKD, amyloidosis, mucositis grade 3/4 and exposure to nephrotoxic drugs are important risk factors. Moderate-to-severe AKI is associated with lower 5-year overall survival. To our knowledge, this is the first study on AKI considering both serum creatinine and urinary output in MM patients undergoing autologous HSCT.
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Acute Kidney Injury in Multiple Myeloma patients undergoing Autologous Hematopoietic Stem Cell Transplant – Cohort study.

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Author´s contributions: NR designed the study, performed data collection, data analysis and interpretation and wrote the manuscript; CB and CC performed data collection and critical revision of the article; CM made critical revision of the manuscript; JAL designed the study and made critical revision of the manuscript.

ABSTRACT

Background: Autologous hematopoietic stem cell transplant (HSCT) plays an important role in multiple myeloma (MM) treatment. Increasing incidence of MM and growing awareness of acute kidney injury (AKI) as a complication of HSCT results in the need to better understand AKI in these patients. We aimed to evaluate incidence, risk factors and 5-year prognostic impact of AKI in MM patients undergoing autologous HSCT.

Methods: Retrospective cohort study. AKI was defined by the KDIGO classification using creatinine and urinary output criteria. We used survival analysis methods considering competing events for risk factors and disease-free survival, Cox proportional regression for overall survival and stepwise regression methods for multivariable models.

Results: We analyzed 143 patients. AKI and moderate-to-severe AKI cumulative incidence was 49.7% and 14.1%, respectively. Urinary output was the first criteria in 18.3%. Factors with independent impact on AKI were higher BMI (HR:1.08;95%CI:1.02-1.13), HCT-CI score≥2 (HR:1.85, 95%CI:1.08-3.17), chronic kidney disease (CKD) (HR:2.06, 95%CI:1.05-4.04), amyloidosis (HR:2.25, 95%CI:1.25-4.06), mucositis grade 3/4 (HR:2.19, 95%CI:1.25-3.86) and exposure to nephrotoxic drugs (HR:2.0856, 95%CI:1.04-4.19). Moderate-to-severe AKI had an impact (HR:1.62, 95% CI:1.15-2.31) on lower 5-year overall survival. No significant impact of AKI was found in lower disease-free overall survival nor in CKD.

Conclusion: AKI affects almost half of MM patients undergoing autologous HSCT and urinary output allows earlier diagnosis in almost a quarter of the patients. Higher BMI, HCT-CI score ≥2, CKD, amyloidosis, mucositis grade 3/4 and exposure to nephrotoxic drugs are important risk factors. Moderate-to-severe AKI is associated with lower 5-year overall survival. To our knowledge, this is the first study on AKI considering both serum creatinine and urinary output in MM patients undergoing autologous HSCT.

Keywords: Acute Kidney Injury; Multiple Myeloma; autologous Hematopoietic Stem Cell Transplant; epidemiology;

INTRODUCTION

Multiple myeloma is the second most common hematological malignancy after non□Hodgkin lymphoma and its incidence has been rising around the globe [1]. Treatment of this malignant monoclonal gammopathy has undergone a significant change in the past two decades resulting in an overall decrease in mortality [2] and autologous hematopoietic stem-cell transplant (HSCT) remains an important part of the treatment of these patients as consolidation therapy after completing conditioning regimen with high-dose chemotherapy [3]. The awareness that a growing number of patients with multiple myeloma is undergoing autologous HSCT brings the need to better characterize and study the prognostic impact of complications associated to this procedure and to analyze them separately from patients undergoing HSCT for other clinical conditions. Acute Kidney Injury (AKI) occurring in the first 100 days after HSCT is a known complication of this procedure and is currently receiving increasing attention as the scientific community continues to stablish a real and significant impact of AKI in a variety of other clinical conditions such as major surgery[4], sepsis[5] and so on.

Unfortunately, the heterogeneity of AKI definitions and the inclusion of patients with different haematologic diagnoses amongst the studies in the early 2000s resulted in a wide range of reported AKI incidence in HSCT. In 2012 the Kidney Disease Improving Global Outcomes (KDIGO) classification for AKI [6] has led to an uniformization of the AKI definition used in all studies on AKI and includes an increase in serum creatinine of at least ≥0.3 mg/dL or ≥50% within 48 hours or urinary output of <0.5 mL/kg/hour for at least 6 hours.

In the last five years AKI considering KDIGO classification has been studied in allogeneic HSCT mainly in patients with leukemia with an AKI incidence varying from 55.1% to 68.9% and prognostic impact with reduced overall survival [7-11]. AKI in autologous HSCT has been less studied since the establishment of the KDIGO classification. Since then, one study in patients with lymphoma suggests an AKI incidence in autologous HSCT of 63.7% with moderate to severe AKI associated with lower overall survival [12] and one study in patients with multiple myeloma refers an AKI incidence calculated only by serum creatinine criteria of 10.3%[13].

The sparse information on AKI incidence according to the KDIGO definition and prognostic impact of this complication in patients with multiple myeloma undergoing autologous HSCT combined with the growing incidence of multiple myeloma enlighten the need for studies on this matter considering AKI definition by KDIGO whilst using both serum creatinine elevation and urinary output reduction.

Our study aims to 1) determine incidence and severity of AKI in patients with multiple myeloma undergoing autologous HSCT using KDIGO classification with both serum creatinine and urinary output criteria, 2) identify independent risk factors for AKI in these patients and 3) evaluate the impact of AKI on overall survival, on disease-free survival, on chronic kidney disease (CKD) and on estimated glomerular filtration rate (eGFR) reduction in the first 5 years after autologous HSCT.

MATERIALS AND METHODS

We performed a single-center retrospective cohort study including all patients with multiple myeloma submitted to autologous HSCT at the Centro Hospitalar Universitário Lisboa Norte, EPE (CHULN, EPE) between January 2005 and December 2015. We excluded patients under the age of 18 years, patients who had received a previous

HSCT, patients with chronic kidney disease already on renal replacement therapy, patients who underwent renal replacement therapy one week before HSCT.

Chemotherapy regimens previous to the transplant included cyclophosphamide, bortezomib and dexamethasone; bortezomib, doxorubicin and dexamethasone; vincristine, doxorubicin and dexamethasone; doxorubicin, thalidomide and dexamethasone; thalidomide and dexamethasone; lenalidomide and dexamethasone.

Cyclophosphamide 3g/m^2) and Granulocyte colony-stimulating factor (10 to 16 μg/kg) were used to mobilize hematopoietic stem cells which were then collected from bone marrow or peripheral blood. Melphalan (dose 140 or 200 mg/m^2 administered in single dose or divided in two days) was used as conditioning regimen and all patients received ciprofloxacin, acyclovir and fluconazole as prophylactic drugs.

We collected data from patients' medical records in our institution from diagnosis period until the first five years of HSCT. We collected demographic variables (age, gender, race, body mass index (BMI)), comorbidity variables (diabetes mellitus, hypertension, CKD, arrythmia, valvular heart disease, ischemic heart disease, cerebrovascular disease, chronic liver disease, intestinal inflammatory disease, peptic ulcer, connective tissue disease, chronic obstructive pulmonary disease, solid-organ cancer, psychiatric disease), multiple myeloma variables (subtype, light chain domain, concomitant amyloidosis, International Staging System classification, cytogenetic abnormalities, bone marrow plasma cells percentage, M-protein level, Serum B2-microglobulin level, number of previous lines of therapy, number of chemotherapy cycles, radiotherapy in the past), HSCT variables (blood results on hospital admission day for HSCT, graft source, period of aplasia, sepsis, fever, shock, nephrotoxic drugs, mucositis, sinusoidal obstructive syndrome, thrombotic microangiopathy, tumor lysis syndrome, AKI, AKI stage) and prognostic impact variables (time to relapse, time to all-cause mortality).

Definitions

Baseline eGFR was estimated according to CKD-EPI equation[14] considering serum creatinine at the last medical appointment before HSCT.

AKI diagnosis was made based on daily values of serum creatinine and 6-hour urinary output since the time of hospital admission for HSCT until hospital discharge, all hospital admissions and weekly evaluations in outpatient clinic in the first 100 days after HSCT. AKI was defined by KDIGO criteria[6] (any of the following: Increase in serum creatinine by $\geq$ 0.3 mg/dl ($\geq$ 26.5 μmol/l) within 48 hours; or increase in serum creatinine to $\geq$ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urinary output <0.5 ml/kg/h for 6 hours). Stage of AKI followed KDIGO classification considering the worst serum creatinine value and/or longest period of urinary volume reduction. Moderate to Severe AKI was defined as AKI stage 2 and AKI stage 3.

CKD was defined according to KDIGO definition[15] as a persistent decrease in eGFR to below 60 mL/min/1.73 m2.

The diagnosis of multiple myeloma was made according the International Multiple Myeloma Working Group (IMWG) Criteria[16]. Multiple myeloma staging was made using International Staging System for Myeloma (ISS)[17]. The associated- AL amyloidosis was diagnosed by demonstration of Congo red staining (kidney or subcutaneous fat biopsy). The Hematopoietic cell transplantation – specific comorbidity index (HCT-CI) was calculated according to the a validated version[18] considering patients comorbidities.

Fever was considered when the measured body temperature was 38ºC (100.4 ºF) or greater. Sepsis was considered when patients presented with temperature ≥38ºC or <36ºC, a white blood cell count >10 000/mm3 or <4000/mm3, and a positive blood culture for bacteria [19]. Shock was considered when patients presented with cardiac frequency > 90 bpm, systolic blood pressure < 90 mmHg and at least one lactate determination > 2mmol/L or 22mg/dL. Oral mucositis was graded according to World Health Organization's (WHO's) Oral Toxicity Scale [20].

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

Ethical Committee The ethical committee of Centro Académico de Medicina de Lisboa approved this study (approval number 35337) according to institutional guidelines and waived the requirement to obtain any informed consent due to its retrospective and non-interventional nature.

Statistical methods

We present categorical variables as frequencies and continuous variables as median and interquartile range (P25 = 25th percentile; P75 = 75th percentile).

Cumulative incidence of AKI, univariable and multivariable analyses of factors predicting AKI were calculated using the Fine and Gray method [21] as survival analysis method considering competing events and death was considered a competing risk event. The final multivariable model was created using backward stepwise regression.

In order to evaluate prognostic impact of AKI, we considered type 1 right censoring for a period of five years after HSCT. The impact of AKI on relapse-free survival was calculated using the Fine and Gray method [21] and death was considered a competing risk event. The final multivariable model was created using backward stepwise regression.

The impact of AKI on overall survival was calculated using cox regression model including demographic variables and other variables with level of significance $\alpha < 0.2$ in univariable analysis 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.

The incidence of CKD and eGFR reduction >25% was calculated at the end of the first year and at the end of the 5 years and the association with AKI in the first 100 days post HSCT was evaluated.

Our approach followed the European Group for Blood and Marrow Transplantation guidelines on statistical methodology [22].A level of significance $\alpha=0.05$ was considered for statistical significance. The statistical software package STATA 16.0 for Windows 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/.) were used for the data analysis.

RESULTS

One hundred and eighty-two patients with MM underwent autologous HSCT during the referred period. Thirty-nine patients presented at least one exclusion criteria. One hundred and forty-three patients were included in our final analysis. Table 1 shows demographic variables, Multiple Myeloma related variables and transplant related variables.

Table 1. Patients' baseline characteristics, Multiple Myeloma characterization and transplant related variables.

Patient's Characteristics and comorbidities	Category	n (%)	P50	P25	P75
Age at transplant (years)			59.2	50.5	63.6
Gender	Female	55 (38.5)			
	Male	88 (61.5)			
Race	caucasian	130 (90.9)			
	non caucasian	13 (9.1)			
BMI (Kg/m2)			26.1	23.4	29.4
HCT-CI	0-1	120 (83.9)			
	≥2	23 (16.1)			
Diabetes Mellitus		18 (12.6)			
Hypertension		53 (37.1)			
Cardiac Heart Failure		10 (7)			
baseline eGFR (ml/min/1.73m2)			100.4	89.5	110.8
Chronic Kidney Disease	eGFR < 60 ml/min/1.73m2	15 (10.5))			
Multiple Myeloma characteristics and previous treatment					
Multiple Myeloma	IgG	90 (62.9)			
	IgA	21 (14.7)			
	IgD	3 (2.1)			
	Free Light Chain Kappa	17 (11.9)			
	Free Light Chain Lambda	12 (8.4)			
Light chain domain	Kappa	87			
	Lambda	51			
Multiple Myeloma and Amyloidosis		5 (3.5)			
ISS	Stage I	70 (49.0)			
	Stage II	38 (26.6)			
	Stage III	35 (24.5)			
Cytogenetic abnormalities		49 (34.3)			
Bone Marrow plasma cells			30	17	67
M-protein level (gr/dl)			3.3	2.2	6.6
Serum B2-microglobulin			3.1	1.7	5.5
Serum Ig (mg/dl)			5880	3490	9200
Light chain (mg/dl)			3560	890	7800
Serum K/L			4.52	0.26	56.35
Nr of previous lines of therapy			1	1	2
Nr of chemotherapy cycles			4	3	4
Radiotherapy in the past		49 (34.5)			
Auto-HSCT characteristics and complications					
Graft source	Peripheral blood	136 (95.1)			
	Bone Marrow	7 (4.9)			
Melphalan	1 day	15 (10.6)			
	2 days	126 (89.4)			
Period of aplasia (days)			11	11	12
Sepsis		38 (26.6)			
Fever		111 (77.6)			
Nephrotoxic drugs		106 (74.1)			
Mucositis	Grade 1-4	80 (55.9)			
	Grade 3-4	16 (11.2)			
TMA/ TLS/ VOD		3 (2.1)			
Shock		4 (2.8)			
At hospital admission day:					
Hemoglobin (gr/dl)			11.7	10.8	12.4
Leukocytes (cells/mm3)			5450	4120	6610
Neutrophils (cells/mm3)			3375	2330	4765
Lymphocytes (cells/mm3)			1066	760	1500
Platelets (/µl)			198000	151000	270000
Urea (mg/dl)			33	28	44
Uric Acid (mg/dl)			5	4.1	6
Calcium (mg/dl)			9.1	8.7	9.4
Phosphate (mg/dl)			3.4	3	2.9
Reactive C Protein (mg/dl)			0.25	0.09	0.67
Lactate Dehydrogenase (U/L)			333	297	390
Albumin			3.9	3.7	4.2
Alanine Transaminase (U/L)			18	14	27
Total Bilirubin (mg/dl)			0.5	0.4	0.6
Serum B2-microglobulin			2.4	1.6	3.1

Legend table 1: P50 – median; P25 – 25th percentile; P75 – 75th percentile; P25 BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; Nr – number; eGFR – estimated glomerular filtration rate;

Ig – immunoglobulin; ISS – International Staging System; TMA/TLS/ TMA/TLS/VOD - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease

Acute Kidney Injury

The AKI cumulative incidence in the first 100 days after HSCT was 49.7% and AKI occurred at a median time of 8 (5-13) days after HSCT. Figure 1. Moderate-to-severe AKI cumulative incidence was 14.1%.

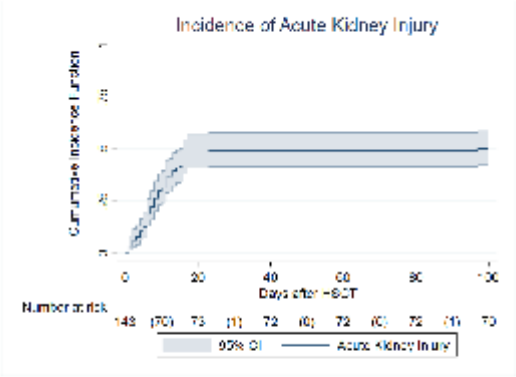

Fig. 1. AKI cumulative incidence function considering death as a competing event.

Considering patients with AKI, the earlier diagnosis criteria for AKI was: serum creatinine elevation in 71.8%; urinary output reduction in 18.3% and both serum creatinine elevation and urinary output reduction in 9.9%.

At presentation, the severity of AKI was stage 1 in 85.9%, stage 2 in 5.6% and stage 3 in 8.5%. The highest severity stage registered was stage 1 in 71.8%, stage 2 in 15.5% and stage 3 in 12.7%.

Acute Kidney Injury risk factors

In the univariable analysis considering death as a competing risk (Table 2) variables associated with AKI were BMI (HR:1.04, 95%CI:1.01-1.11; p=0.048), HCT-CI score ≥2 (HR:2.06, 95%CI:1.24-3.43; p=0.005), baseline eGFR (HR:0.98, 95%CI:0.97-0.99; p<0.001), CKD (HR:3.3, 95%CI:1.62-6.71; p=0.001), ISS (HR:1.55, 95%CI:1.18-2.04; p=0.002), fever (HR:2.01, 95%CI:1.02-3.97; p=0.044), sepsis (HR:1.78, 95%CI:1.11-2.85; p=0.016), nephrotoxic drugs (HR:2.56, 95%CI:1.30-5.06; p=0.007), Mucositis (HR:1.91, 95%CI:1.16-3.14; p=0.001), Mucositis grade 3 and 4 (HR:2.94, 95%CI:1.75-4.92; p<0.001).

Table 2. Competitive risk regression. Univariable analysis for AKI.

Patient`s Characteristics and comorbidities	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Age at transplant (years)	1.02	1.00	1.05	0.057
Gender (reference Female)	1.24	0.77	1.99	0.379
Race (reference non caucasian)	1.18	0.54	2.57	0.684
BMI (Kg/m2)	1.04	1.00	1.10	0.048
HCT-Ci≥2	2.06	1.24	3.43	0.005
Diabetes Mellitus	1.57	0.88	2.79	0.120
Hypertension	1.19	0.75	1.90	0.462
Cardiac Heart Failure	1.63	0.80	3.31	0.175
baseline eGFR (ml/min/1.73m2)	0.98	0.97	0.99	<0.001
Chronic Kidney Disease	3.3	1.62	6.71	0.001
Multiple Myeloma characteristics and previous treatment				
Light Chain domain (reference lambda)	1.18	0.72	1.92	0.508
Multiple Myeloma and Amyloidosis	2.12	0.92	4.94	0.078
ISS	1.55	1.18	2.04	0.002
Cytogenetic abnormalities	1.56	0.99	2.46	0.055
Bone Marrow plasma cells	1.00	0.99	1.01	0.96
M-protein level (gr/dl)	0.99	0.94	1.03	0.609
Serum B2-microglobulin	1.04	1.00	1.08	0.114
Nr of previous lines of therapy	1.25	0.82	1.92	0.288
Nr of chemotherapy cycles	0.92	0.77	1.1	0.375
Radiotherapy in the past	1.18	0.74	1.87	0.484
HSCT characteristics and complications				
Graft source	1.24	0.40	3.88	0.711
Melphalan (reference 1 day)	1.26	0.63	2.54	0.513
Period of aplasia (days)	1.03	0.95	1.1	0.500
Sepsis	1.78	1.11	2.85	0.016
Fever	2.01	1.02	3.97	0.044
Nephrotoxic drugs	2.56	1.30	5.06	0.007
Mucositis 1-4	1.91	1.16	3.14	0.010
Mucositis 3-4	2.94	1.75	4.92	<0.001
TMA/ TLS/ VOD	0.69	0.73	6.43	0.741
Shock	2.61	0.69	9.85	0.157
At hospital admission day:				
Hemoglobin (gr/dl)	0.9	0.76	1.06	0.219
Leukocytes (cells/mm3)*	1.02	0.99	1.03	0.157
Neutrophils (cells/mm3)*	1.02	1.00	1.03	0.021
Lymphocytes (cells/mm3)	0.99	0.99	1.00	0.302
Platelets (/µl)	0.99	0.99	1.00	0.426
Urea (mg/dl)	1.03	1.02	1.04	<0.001
Uric Acid (mg/dl)	1.01	0.97	1.05	0.759
Calcium (mg/dl)	0.74	0.49	1.10	0.141
Phosphate (mg/dl)	0.68	0.47	0.99	0.049
Reactive C Protein (mg/dl)	0.99	0.93	1.06	0.824
Lactate Dehydrogenase (U/L)**	1.06	1.02	1.10	0.002
Albumin	1.01	0.94	1.08	0.874
Alanine Transaminase (U/L)	0.98	0.96	1.00	0.077
Total Bilirubin (mg/dl)	0.65	0.25	1.69	0.380
Serum B2-microglobulin	1.04	0.99	1.08	0.114

Legend table 2: BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index; eGFR – estimated glomerular filtration rate; ISS – International Staging System; Nr – number; TMA/TLS/VOD - thrombotic microangiopathy, tumor lysis syndrome or veno-occlusive disease.

Variables independently associated with a higher incidence of AKI are shown in Table 3 and included BMI (HR:1.08, 95%CI:1.02-1.13; p=0.004), HCT-CI score ≥2 (HR:1.85, 95%CI:1.08-3.17; p=0.025), CKD (HR:2.06, 95%CI:1.05-4.04; p=0.035), Multiple Myeloma and Amyloidosis (HR:2.25, 95%CI:1.25-4.06; p=0.007), Mucositis grade 3 and 4 (HR:2.19, 95%CI:1.25-3.86; p=0.006) and nephrotoxic drugs (HR:2.0856, 95%CI:1.04-4.19; p=0.039). Table 3.

Table 3. Competing risks multivariable regression analysis for AKI.

Patient's and transplant related variables	Hazard ratio estimate	95% confidence interva		p-value
		lower limit	upper limit	
BMI (Kg/m2)	1.08	1.02	1.13	0.004
HCT-CI ≥2	1.85	1.08	3.17	0.025
Chronic Kidney Disease	2.06	1.05	4.04	0.035
Multiple Myeloma and Amyloidosis	2.25	1.25	4.06	0.007
Mucositis Grade 3 and 4	2.19	1.25	3.86	0.006
Nephrotoxic drugs	2.08	1.04	4.19	0.039

Legend table 3: BMI - body mass index; HCT-CI - hematopoietic stem cell transplant comorbidity index.

Overall survival and relapse-free survival

The median overall survival was 18.7 months. In the first year after HSTC, 14 (9.7%) patients had died. At the end of the 5-year follow-up period 51 (35.7%) patients had died.

In univariable analysis, variables with an impact on lower overall survival were moderate to severe AKI (HR:1.95;95%CI:1.26-2.98; p=0.040) (figure 2), ISS (HR:1.69;95%CI:1.22-2.35;p=0.002), cytogenetic abnormalities (HR:2.21;95%CI:1.27-3.83;p=0.005) and relapse (HR:1.25 ;95%CI:0.71-2.19;p=0.043).

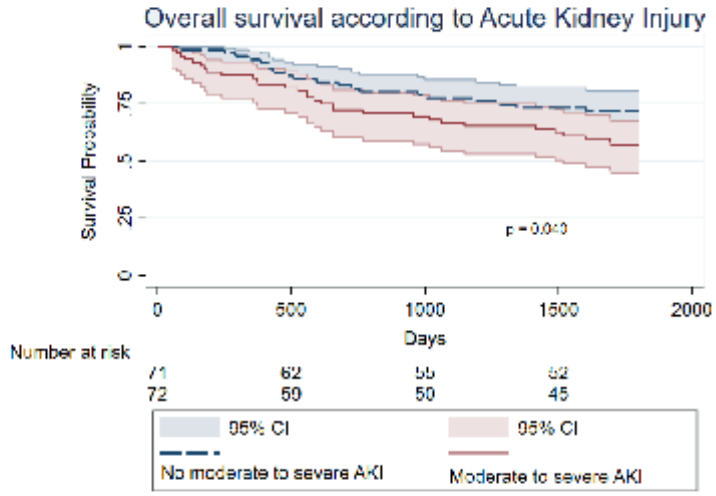

Fig 2. Overall survival in days according to moderate to severe AKI.

In our multivariable model, variables with an independent impact on lower overall survival were diabetes mellitus (HR:3.29.76, 95% CI:1.01-9.72), relapse (HR:3.05, 95% CI:1.12-8.31), cytogenetic abnormalities (HR:2.36, 95% CI:1.01-5.53), moderate to severe AKI (HR:1.62, 95% CI:1.15-2.31) and BMI (HR:1.10, 95% CI:1.00-1.21). Table 4.

Table 4. Multivariable Cox regression for mortality.

Variables	Hazard ratio estimate	95% confidence interval		p-value
		lower limit	upper limit	
Age at transplant (years)	0.98	0.94	1.04	0.711
Gender (reference Female)	0.52	0.20	1.30	0.160
BMI (Kg/m2)	1.10	1.00	1.21	0.045
Diabetes Mellitus	3.29	1.01	9.72	0.048
Hypertension	1.04	0.97	1.02	0.807
Moderate to Severe AKI	1.62	1.15	2.31	0.045
ISS stage	1.67	0.89	3.14	0.113
Cytogenetic abnormalities	2.36	1.01	5.53	0.049
Serum B2-microglobulin at diagnosis	1.02	0.95	1.09	0.564
Relapse	3.05	1.12	8.31	0.029

Legend table 4: BMI - body mass index; AKI – Acute Kidney Injury; ISS – International Staging System.

The cumulative relapse incidence was 61.8% five years after HSCT. The median disease-free overall survival was 43.6 months. No statistically significant association was found between AKI (nor moderate-to-severe AKI neither severe AKI) with lower disease-free overall survival.

CKD and loss of renal function

The median eGFR previous to HSCT was 100.4 (89.5-110.8) mL/min/1.73 m2 and 10.5% of patients had CKD.

At the end of the first year, the median eGFR was 88.6 (68.6-103.3) mL/min/1.73m2, an eGFR reduction > 25% was verified in 18.4% of the patients and CKD prevalence was 17.5%. At the end of the five years, the median eGFR was 82. 6 (60.5-94.8) mL/min/1.73 m2, an eGFR reduction > 25% was verified in 32.1%of the patients and CKD prevalence was 27.5%.

No statistically significant association was found between AKI in the first 100 days after HSCT and eGFR reduction > 25% (p=0.819) nor CKD prevalence (p=0.101).

DISCUSSION

In this study, we analyzed incidence and variables related to AKI in patients with multiple myeloma undergoing autologous HSCT and the impact of this complication on overall survival, relapse-free survival and chronic kidney disease. We did so by considering the most updated AKI definition – the KDIGO classification[6] – using both serum creatinine criteria and urinary output criteria.

We found an AKI cumulative incidence of 49.7% and a moderate-to-severe AKI cumulative incidence of 14.1%. Considering other studies on AKI in autologous HSCT Caliskan et al reported and AKI incidence of 52%[23] in populations with several hemato-oncologic diagnosis, Fadia et al reported a moderate-to-severe AKI incidence of 21%[24] in a population with AL amyloidosis, Merouani et al reported an AKI incidence of 56%[25] in a population with breast cancer, Rodrigues et al reported an AKI incidence of 63.7%[12] in a population with lymphoma and Andronesi et al reposted an AKI incidence of 10.4% [13] in a population with multiple myeloma. The range of these results is related to different AKI definitions in the older studies, omission of the urinary output criteria in most recent studies and the heterogeneity of diagnoses amongst studies - each with its own disease and treatment burden contributing differently for AKI. We were already expecting to have lower moderate-to-severe AKI incidence in our study compared to the AL amyloidosis population study as the presence of amyloidosis was itself an independent risk factor for AKI in our study. We were also expecting to have lower AKI incidence compared to populations with lymphoma or breast cancer, where the previous high dose chemotherapy regimens are itself related to higher nephrotoxicity and the performance of autologous HSCT is not a first line procedure but more often used when the disease relapses or progresses despite chemotherapy regimens. We believe our higher AKI incidence compared to Andronesi et al in the multiple myeloma population can be explained by the fact that we included not only serum creatinine criteria but also urinary output criteria, we considered an incidence period of 100 days after HSCT instead of the 30 days referred in their study and our population was older.

In our study, the AKI diagnosis was made firstly by urinary output reduction in 18.3% of AKI cases. This finding points out the importance to monitor urinary output in these patients and should be taken in account in clinical practice to approach AKI as soon as possible.

According to our results, the most important factors with impact on AKI are higher BMI, an HCT-CI score ≥2, chronic kidney disease prior to HSCT, the concomitant presence of amyloidosis, developing mucositis grade 3 and 4 and the exposure to nephrotoxic drugs.

Higher BMI has been pointed out as a risk factor in other clinical scenarios by Gameiro et al [26] and Billings et al [27] in critically ill and septic patients and in patients undergoing cardiac surgery, respectively. The association between BMI and AKI has been explained by the adipose production of inflammatory mediators (adipokines, leptin) and decreased production of adiponectin in response to acute illness, which increases susceptibility to AKI[28].

A score equal or superior to 2 in the HCT-CI was associated to higher risk to develop AKI in our study, which has also mentioned by studies on AKI in allogeneic HSCT [11]. This comorbidity index has been validated for autologous HSCT [29] and we believe it should be taken in consideration as an important tool also for predicting AKI.

CKD conferred more than twofold higher risk of developing AKI in our study and has also been referred by Andronesi et al[13] in autologous HSCT population. In the last decade, CKD has been recognized as a clear risk factor for AKI in general[30], as it results in reduced renal reserve and inability to handle stress such as abnormally low blood pressure or nephrotoxic drugs.The presence of amyloidosis was also associated to a higher risk of AKI, which we explain by renal deposition of amyloid reducing the capacity of adaptive response to an insult, making the kidney more susceptible to acute kidney injury.

Mucositis grade 3 and 4 conferred more than twofold higher risk of developing AKI according to our results. This finding was also referred by Andronesi et al[13] and Rodrigues et al[12] in autologous HSCT studies and is explained mainly by the extracellular volume depletion as a consequence of vomiting and diarrhea.

In our study, AKI did not have an impact on overall survival but moderate to severe AKI was independently associated with lower overall survival (HR:1.95;95%CI:1.26-2.98) during the first 5 years after HSCT. AKI had no impact on disease-free survival nor eGFR reduction, nor on chronic kidney disease progression.

Although the impact of AKI on overall survival was not consistently found in HSCT studies, a meta-analysis by Kanduri et al[7] on the matter concluded an impact on 3-month mortality and 3-year mortality, with higher impact in more severe stages, which we believe is reinforced by our study with even longer follow up. Also, by observing that the stage at the onset of AKI was not always the highest stage reached during AKI episodes (stage 1,2 and 3 at the onset represented 85.9%, 5.6% and 8.5%, respectively, but at the day of the worst measure represented 71.8%, 15.5% and 12.7%, respectively), we reinforce the need for an earlier diagnostic and therapeutic approach.

Before undergoing HSCT our patients had a median eGFR of 100.4 (89.5-110.8) mL/min/1.73 m^2 and five years later, the survivors had a median eGFR of 82.6 (60.5-94.8) mL/min/1.73 m^2, which represents a much higher eGFR reduction than the known 1 mL/min/m^2 per year of the general population. The CKD prevalence before undergoing HSCT was 10.5% and at the end of the five years CKD prevalence amongst the survivors was 27.5%. Although we did not stablish a significant association between AKI and these outcomes we consider these

findings extremely relevant and we emphasize the need to start preventive measures and monitorization during follow-up.

The retrospective nature of our study is related to limitations concerning external validity and data availability. Patients were often exposed to more than one nephrotoxic at the same time which makes it difficult to identify the impact of each drug on AKI. Also, no data was available on structural abnormalities of the kidneys nor proteinuria during follow-up as other criteria for CKD.

Still, to the best of our knowledge this is the first study using KDIGO classification with both creatinine criteria and urinary output criteria to analyze AKI in patients with multiple myeloma undergoing autologous HSCT. Prospective and multicentric studies are needed to study AKI in this growing population in order to provide better care to our patients.

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DATA AVAILABILITY STATEMENT - The data underlying this article will be shared on reasonable request to the corresponding author.

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