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Pharmacological Nephrotoxicity Profile in a Comprehensive Cancer Center: What Changed in Two Decades and Predictors for the Need for Haemodialysis and Mortality

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Abstract

Introduction and objectives

Acute kidney injury (AKI) is a frequent and severe complication in hospitalised cancer patients. However, overall data from in-hospital drug-related AKI in cancer patients is scarce. We aim to review the profile of moderate to severe drug-induced AKI in patients admitted to an oncology hospital over the last two decades and to assess renal and overall outcomes.

Material and methods

410 cases of drug-induced AKI KDIGO≥ 2 were analysed, comparing between two decades from 2002 to 2021 in a comprehensive cancer center.

Results

The main differences were the introduction of new classes of cancer therapy (e.g., immune checkpoint inhibitors [ICPI] and tyrosine kinase inhibitors [TKI]), a decrease in

nephrotoxicity due to platinum-based drugs, and an increase in nephrotoxicity caused by multiple drugs without cancer-directed therapy. Mortality was similar, but the need for haemodialysis (HD) was higher in the second decade (25,5% vs 36,6%, p= 0,02). Multivariate analysis presented invasive mechanical ventilation and sepsis as risk factors for both HD and mortality, haematologic cancer as risk factors for HD, and the need for HD and multiple drugs without cancer-directed therapy as risk factors for mortality.

Conclusion

Adequate drug surveillance and prophylaxis render cancer therapy as a relatively small contributor to drug-induced AKI in a comprehensive cancer center. Critically ill patients have a higher need for HD and mortality regardless of the nephrotoxic agent implied.

Keywords: acute kidney injury; drug nephrotoxicity; onco-nephrology; cancer patients; haemodialysis; mortality

Introduction

Acute kidney injury (AKI) is a frequent and severe complication in hospitalised cancer patients, leading to increased morbidity, mortality, and healthcare costs[1]. In a Danish population observational study including 1.2 million people followed from 1999 to 2006, the 1- and 5-year risks of AKI and acute kidney failure (defined by the RIFLE criteria) were 17.5% and 27%, and 4.5% and 7.6%, respectively; the risk varied depending on the type of cancer and respective treatments employed[2]. AKI in these patients is particularly concerning because it alters both the pharmacokinetics and pharmacodynamics of anti-cancer drugs, resulting in increased risk for drug-associated toxicities, sometimes contraindicating them, and compromises both the efficacy of oncologic therapies and the patient's overall prognosis[3]. One of the most expected contributors to AKI in cancer patients is nephrotoxicity induced by antineoplastic agents. While these drugs are effective in targeting malignancies, many are known to exert toxic effects on renal structures, exacerbating the risk of AKI and often necessitating the use of renal replacement therapies (RRT) such as haemodialysis (HD)[4]. However, apart from one paper from this group[5], no other studies have directly shown the relative impact of antineoplastic drugs related toxicity on the overall burden of nephrotoxicity in a comprehensive cancer center (i.e. an accredited cancer center with expertise in cancer research and in providing services directly to cancer patients).

Antineoplastic drugs and nephrotoxicity

Antineoplastic agents can exert nephrotoxic effects through diverse mechanisms, including direct tubular damage, glomerular injury, and alterations in renal hemodynamics. Over the years, the spectrum of kidney diseases in cancer patients has changed, mainly as a result of modifications to the cancer treatment regimens[6]. Nephrotoxicity can occur with various classes of antineoplastic agents, such as platinum-

based compounds (e.g., cisplatin), anthracyclines (e.g., doxorubicin), alkylating agents (e.g., ifosfamide), and targeted therapies such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICPI)[4,7,8]. Cisplatin is classically notorious for its nephrotoxic potential, causing dose-dependent renal tubular injury and apoptosis, particularly in the proximal tubules[9]. Other agents, such as methotrexate, may lead to nephrotoxicity through crystalluria and obstructive nephropathy[4], whereas drugs like bevacizumab, a vascular endothelial growth factor inhibitor, can induce thrombotic microangiopathy, which results in glomerular injury[7,10]. In addition to these, TKI and ICPI are two of the most expanding drug groups in oncology, whose nephrotoxic properties are being thoroughly studied, both causing AKI through several mechanisms. While the most common mechanisms of AKI due to TKI are podocytopathies and thrombotic microangiopathy[11], ICPI causes primarily immune-mediated acute tubulointerstitial nephritis, although other mechanisms may also be implied, whether tubular, vascular, or glomerular in nature[12].

The complex interplay between cancer treatment, nephrotoxicity, and AKI underscores the importance of early identification and management of renal complications in oncology patients. Several strategies have been proposed to mitigate the risk of nephrotoxicity, including dose adjustments, hydration protocols, and using nephroprotective agents such as amifostine to prevent cisplatin nephrotoxicity[13]. Despite these measures, the prevention of AKI remains challenging and once established, AKI significantly worsens patient outcomes.

Haemodialysis in cancer patients with nephrotoxic AKI

In cancer patients, the decision to initiate dialysis is particularly complex, as it must account not only for the severity of renal dysfunction but also for the patient's overall prognosis and cancer trajectory. Patients with AKI who require HD in oncology settings

have significantly higher mortality rates than those who do not[14]. The need for RRT is further complicated by the common presence of factors such as infection, tumour lysis syndrome, or concurrent administration of other nephrotoxic agents[3,15]. Moreover, oncologic treatments may have to be delayed or adjusted in patients requiring dialysis, potentially affecting cancer outcomes[2].

While RRT can be lifesaving by managing the complications of severe AKI, its use in cancer patients is associated with substantial morbidity, prolonged hospital stays, and increased healthcare costs. Additionally, the initiation of dialysis in patients with terminal cancer or poor performance status is a subject of ethical debate, as the burden of dialysis may outweigh the potential benefits in these cases.

Mortality and outcomes in cancer patients with nephrotoxic AKI

A poor prognosis is generally observed in cancer patients who develop nephrotoxic AKI, especially those requiring HD. In critically ill cancer patients, mortality rates associated with AKI are significantly high, with studies indicating in-hospital mortality rates ranging from approximately 50% to as high as 70%, particularly among patients with metastatic disease, sepsis, or multi-organ failure. Haematologic malignancies and high SOFA scores (indicating organ dysfunction severity) are also linked to poorer outcomes. Patients with solid tumours requiring RRT or intensive care unit (ICU) admission experience mortality rates exceeding 70% in some cases, exacerbated by conditions like tumour lysis syndrome and exposure to nephrotoxic treatments[3,16,17].

Study aims and rationale

Data from drug-related AKI in cancer patients is scarce. In this setting, we aim to review the profile of moderate to severe nephrotoxic AKI in patients admitted to an oncology hospital over the last two decades, explore the clinical scenarios in which AKI progresses

to require RRT, and examine the associated mortality rates in cancer patients. Understanding these dynamics is crucial for clinicians in oncology, as preventing or mitigating nephrotoxicity could enhance patient outcomes, maintain continuity of cancer treatment, and reduce the burden on healthcare systems.

Material and methods

Study population and design

In this retrospective cohort study, we included all patients hospitalised in a comprehensive cancer center during the period from January 2002 to December 2021 with the diagnosis of AKI KDIGO≥ 2 needing evaluation by the Nephrology Department, which primary aetiology was drug-induced nephrotoxicity. We excluded all patients for whom complete data could not be collected and patients enrolled in randomised controlled trials. A sub-analysis of the two decades of study time (first decade, 2002 to 2011 vs second decade, 2012 to 2021) was carried out (see Supplementary material: Figure S1).

Statistical analysis

The data was collected from the hospital information system. In descriptive analyses, we analysed sociodemographic data, oncological data, nephrotoxicity data, clinical factors associated with AKI, and hospitalisation outcomes. The normality test Kolmogorov-Smirnov was performed for continuous variables, demonstrating a non-normal distribution. Comparative analysis of all variables was made using non-parametric tests: bivariate inferential analysis was made with Mann-Whitney U test for continuous variables and Pearson's chi-squared test for categorical variables; multivariate analysis was made with logarithmic regression with stepwise forward method, assessing the

models' goodness of fit with Nagelkerke pseudo-R2. Statistical significance was considered for p-value <0,05. Statistical analysis was conducted using SPSS® version 28.0.

Study oversight

The study was approved by the institution's Medical Ethics Committee (ref. no. 015/024). No data on patients' personal information was recorded, and their identities were protected.

Results

Study population

Figure S1 (Supplementary material) depicts the flow chart for sample selection. We collected data on 2042 inpatients whose diagnosis of AKI KDIGO≥ 2 were made and selected 584 in which the primary aetiology for AKI was drug-induced nephrotoxicity. In total, 174 were excluded due to incomplete data. The final study population was 410 patients; the sub-analysis comparing the two decades of the study comprised 137 patients in the first decade and 273 patients in the second decade. There was an asymmetric eligibility between the study's first and second decade, as seen in Figure S1 (Supplementary material).

Overall characterisation

Table 1 summarises demographic and clinical data.

Demographic data

Overall, 243 patients (62%) were male, with a median age of 61 years [interquartile range (IQR) 48-71].

Oncologic data

The most prevalent cancers were haematologic (n= 178; 43,4%), gastrointestinal (n= 73; 17,8%), urologic (n= 42, 10,2%), head and neck (n= 30, 7,3%), and lung cancer (n= 20, 4,9%), as shown on Table 1. Only 12 patients (0,5%) had evidence of more than one cancer. No data on cancer status and line of therapy was adequately available.

Of the 178 haematologic cancer patients, 89 (21,7%) were submitted to bone marrow transplant (BMT), of which 39 (9,5%) were allogeneic BMT and 50 (12,2%) were autologous BMT.

AKI related factors

Several factors were contemplated as contributors to AKI besides the nephrotoxic drugs (regarded as the primary cause of AKI in this study cases). The most prevalent factor by far was sepsis (n= 142, 34,6%), followed by pre-renal causes (n= 39, 9,5%) and other factors directly related to cancer and its treatments, such as graft-versus-host disease (GVHD; n= 35, 8,5%), obstructive causes (n= 34, 8,3%), postoperative status (n= 20, 4,9%), tumour lysis syndrome (n= 15, 3,7%), hypercalcemia (n= 14, 3,4%) and tumoral infiltration (n= 7, 1,7%).

Nephrotoxic agents

Table 2 shows the frequency of the nephrotoxic drug group implicated in each case per decade (discussed below); Table S1 (Supplementary material) lists the nephrotoxic drugs implicated, alone or in combination. Overall, 147 (35,9%) cases involved multiple drugs (up to 7 potentially nephrotoxic drugs in the same patient) and 263 (64,1%) involved a single nephrotoxic drug. In the multiple drugs group, the most common agents involved were the antimicrobials (in 70 cases, 17,1% [not shown]), whether a combination of antibiotics, antivirals, or antifungals. In the single nephrotoxic group, NSAIDs were the

most common cause (n= 79, 19,3%).

Nephrological and global outcomes

Regarding renal outcomes, 135 (32,9%) patients needed RRT due to drug nephrotoxicity, 81 (19,8%) with continuous HD in ICU.

Regarding global outcomes, 104 (25,4%) patients needed invasive mechanical ventilation (IMV) in ICU. A total of 121 (29,5%) patients died following drug nephrotoxicity.

Evolution through time – first vs second decade comparison

Demographic Data

Gender distribution was similar between the two decades (59,9% vs 63,0%, p= 0,536), with a higher proportion of men. The patients' median age was higher in the second decade (59 [IQR 42-69] vs 62 [IQR 51-71] years old, p= 0,027).

Oncologic data

The overall distribution of cancer group types in patients with drug nephrotoxicity was similar between the two decades (p= 0,906), with haematologic (43,8% vs 43,2%) and gastrointestinal (16,1% vs 18,7%) cancers covering over half the cancers. There was no data on cancer multiplicity per patient in the first decade to allow comparison.

Concerning haematologic patients' treatment with BMT, there was no statistically significant difference in overall BMT (20,5% vs 24,1%, p= 0,408). However, there was a lower proportion of autologous BMT and a higher proportion of allogeneic BMT in the second decade (18,3 vs 9,2% and 5,8% vs 11,3%, respectively, p= 0,004).

AKI related factors

There was a statistically significant difference in the two most prevalent AKI-related factors – sepsis and pre-renal causes – both being higher in the second decade (27,0% vs 38,5%, p= 0,021, and 3,6% vs 9,2%, p= 0,043, respectively). There was no statistically significant difference in the other tested AKI-related factors (Table 1).

Nephrotoxic agents

Analysing Table S1 (Supplementary material), it is evident that several drugs and drug groups were not the cause of AKI in the first decade but were in the second decade, particularly some antibiotics (e.g. colistin), bisphosphonates, and newer groups of anti-cancer therapies, namely ICI, TKI and other targeted therapy drugs like vemurafenib and cetuximab.

Regarding the nephrotoxic agents implicated in each case by drug group (Table 2), there was a lower proportion of platinum-based drugs in the second decade (10.2% vs 8.1%, p= 0.020). There was an increase in cases due to multiple drugs not involving cancer-directed therapy (16.8%, vs 28.2%, p= 0.011), mainly combinations of antibiotics, antivirals, or antifungals (not shown). There was no difference in the number of drugs implicated in each case (median 1 [IQR 1-2] vs 1 [IQR 1-2], p= 0,061).

Nephrological and global outcomes

Regarding nephrological outcomes, the need for RRT increased in the second decade (25,5% vs 36,6%, p=0,024), with no difference in the practice of continuous HD (16,1% vs 21,6%, p=0,183) or intermittent HD (12,4% vs 19,8%, p=0,052).

Regarding global outcomes, there were no statistically significant differences in the need for IMV in ICU setting (24,1% vs 26,0%, p= 0,673) or in mortality (24,8% vs

31,9%, p= 0,140) between the two decades.

Predictors of the need for haemodialysis in patients hospitalised with drug-induced AKI

Every demographic and clinical variable was evaluated as possible risk factor for the need for RRT.

Bivariate analysis

Demographic status. In the bivariate analysis (Table 3), patients needing RRT were younger (median 53 [IQR 38-64] vs 64 [IQR 54-73] years old, p< 0,001 [not shown in Table 3]). We did not find a statistical difference in the need for RRT between genders (p= 0,569).

Cancer status. The need for RRT was higher in haematologic cancer (59,0% vs 12,9%, odds ratio [OR] 9,69 [95% confidence interval (CI) 5,96-15,75], p< 0,001) or when patients got BMT (68,5% vs 23,1%, OR 7,27 [95% CI 4,24-12,20], p< 0,001), while it was lower in several solid tumours, namely breast (0% vs 34,4%, p= 0,003), gastrointestinal (17,8% vs 36,2%, OR 0,38 [95% CI 0,20-0,72], p= 0,002), gynaecologic (5,3% vs 34,3%, OR 0,11 [95% CI 0,01-0,91], p= 0,009), head and neck (6,7% vs 35,0%, OR 0,13 [95% CI 0,03-0,57], p= 0,001), lung (10,0% vs 34,1%, OR 0,22 [95% CI 0,05-0,94], p= 0,025) and urologic cancer (16,7% vs 34,8%, OR 0,36 [95% CI 0,16-0,87], p= 0,002). Patients with more than one cancer did not show a statistical difference in the need for RRT (p= 0,976).

Other clinical factors related to AKI. There was a higher need for RRT in patients with GVHD (71,4% vs 29,3%, OR 6,02 [95% CI 2,80-12,96], p< 0,001) and sepsis (66,2% vs

15,3%, OR 10,84 [95% CI 6,70-17,54], p< 0,001), while other factors had no difference or had a lower need for RRT, such as patients with concomitant pre-renal AKI (6,7% vs 35,0%, OR 0,13 [95% CI 0,03-0,57], p= 0,001), concomitant post-renal AKI (17,6% vs 34,3%, OR 0,41 [95% CI 0,17-1,02], p= 0,048) and post-operatory status (10,0% vs 34,1%, OR 0,22 [95% CI 0,05-0,94], p= 0,025). The need for IMV also had a higher need for RRT (81,7% vs 16,3%, OR 22,90 [95% CI 12,80-41,00], p< 0,001).

Nephrotoxic drug groups. The need for HD was higher when antiviral drugs (66,7% vs 31,6%, OR 4,07 [95% CI 1,45-12,90], p= 0,005), calcineurin inhibitors (CNI; 64,3% vs 31,8%, OR 3,86 [95% CI 1,27-11,75], p= 0,011), and when multiple drugs without cancer-directed therapy (62,0% vs 23,5%, OR 3,32 [95% CI 2,35-4,70], p< 0,001) were implicated. On the other hand, ICPI (7,7% vs 33,8%, OR 0,16 [95% CI 0,20-1,27], p= 0,049), non-steroidal anti-inflammatory drugs (8,9% vs 38,7%, OR 0,15 [95% CI 0,07-0,35], p< 0,001), platinum-based therapy (13,9% vs 34,8%, OR 0,30 [95% CI 0,12-0,80], p= 0,011), and multiple drugs with cancer-directed therapy (13,0% vs 34,1%, OR 0,29 [95% CI 0,09-0,99], p= 0,037) were less likely to precipitate the need of HD.

Multivariate analysis

Multivariable analysis was performed to generate a predictive model based on risk factors for the need for RRT. Two analyses were conducted: one solely assessing the risk factor within the several drug groups and another one with every assessed factor. The drug group model entered the following predictors: antibiotic drug (OR 2,04 [95% CI 1,04-4,00], p= 0,038), antiviral drug (OR 8,54 [95% CI 2,70-27,11], p< 0,001), CNI (OR 7,69 [95% CI 2,38-24,85], p< 0,001), and multiple drugs without cancer-directed therapy (OR 6,97 [95% CI 3,87-12,54], p< 0,001) as risk factors for the need of RRT, and NSAID (OR 0,42 [95% CI 0,17-1,01], p= 0,052) as a protective factor for the need of RRT (Table 4). The

model's Nagelkerke pseudo-R2 of 0,267 indicates a moderate relationship between the predictors and the need for RRT.

The overall model entered the following predictors: haematologic cancer (OR 3,27 [95% CI 1,82-5,90], p< 0,001), sepsis (OR 2,18 [95% CI 1,08-4,41], p= 0,030), and IMV (OR 7,46 [95% CI 3,31-16,80], p< 0,001) as risk factors for the need of RRT (Table 5). The model's Nagelkerke pseudo-R2 of 0,471 indicates a strong relationship between the predictors and RRT.

Predictors for mortality in patients hospitalised with drug-induced AKI

Bivariate analysis

Demographic status. In the bivariate analysis (Table 6), patients with fatal outcomes were younger (median 54 [IQR 38-65] vs 63 [IQR 53-73] years old, p< 0,001 [not shown in Table 6]). We did not find a statistical difference in mortality between genders (p= 0,498).

Cancer status. Mortality was higher in haematologic cancer (53,9% vs 10,8%, OR 9,69 [95% CI 5,83-16,13], p< 0,001) or when they got BMT (64,0% vs 19,9%, OR 7,14 [95% CI 4,29-11,94], p< 0,001), while it was lower in several solid tumours, namely breast (0% vs 30,8%, p= 0,006), gastrointestinal (12,3% vs 33,2%, OR 0,28 [95% CI 0,14-0,59], p< 0,001), gynaecologic (0% vs 30,9%, p= 0,004), head and neck (6,7% vs 31,3%, OR 0,16 [95% CI 0,04-0,67], p= 0,004), and urologic cancer (14,3% vs 31,3%, OR 0,37 [95% CI 0,15-0,90], p= 0,022). Patients with more than one cancer did not show a statistical difference in mortality (p= 0,349).

Other clinical factors related to AKI. There was higher mortality in patients with GVHD (60,0% vs 26,7%, OR 4,12 [95% CI 2,02-8,42], p< 0,001), sepsis (64,1% vs 11,2%, OR 14,16 [95% CI 8,49-23,61], p< 0,001), and tumour lysis syndrome (53,3% vs 28,6%, OR 2,85 [95% CI 1,01-8,05], p= 0,039), while concomitant pre-renal AKI was associated

with lesser mortality (13,3% vs 30,8%, OR 0,35 [95% CI 0,23-1,01], p= 0,044) and no other factor had a statistically significant difference in mortality. The need for IMV was also associated with higher mortality (79,8% vs 12,4%, OR 27,90 [95% CI 15,50-50,10], p< 0,001), as well as the need for RRT was (61,5% vs 13,8%, OR 9,96 [95% CI 6,12-16,21], p< 0,001).

Nephrotoxic drug groups. Mortality was higher when antiviral drugs (53,3% vs 28,6%, OR 2,85 [95% CI 1,01-8,05], p= 0,039) and multiple drugs without cancer-directed therapy (67,0% vs 17,4%, OR 9,63 [95% CI 5,78-16,03], p< 0,001) were implicated. On the other hand, antibiotic drugs (16,9% vs 31,9%, OR 0,44 [95% CI 0,22-0,87], p= 0,015), iodinated contrast (10,0% vs 31,1%, OR 0,25 [95% CI 0,07-0,83], p= 0,015), non-steroidal anti-inflammatory drugs (8,9% vs 34,4%, OR 0,19 [95% CI 0,08-0,42], p< 0,001), and platinum-based therapy (11,1% vs 31,3%, OR 0,28 [95% CI 0,10-0,79], p= 0,011) had lower mortality.

Multivariate analysis

Multivariable analysis was performed to generate a predictive model based on risk factors for mortality, as conducted for RRT (see above). The drug group model entered the following predictors: antifungal drug (OR 20,08 [95% CI 2,03-198,34], p= 0,010), antiviral drug (OR 7,65 [95% CI 2,62-22,38], p< 0,001), CNI (OR 6,69 [95% CI 2,22-20,21], p< 0,001), and multiple drugs without cancer-directed therapy (OR 13,59 [95% CI 7,89-23,43], p< 0,001) as risk factors for mortality (Table 7). The model's Nagelkerke pseudo-R2 of 0,340 indicates a moderate relationship between the predictors and mortality.

The overall model entered the following predictors: IMV (OR 3,25 [95% CI 1,69-6,22], p< 0,001), multiple drugs without cancer-directed therapy (OR 6,97 [95% CI 3,87-12,54], p< 0,001), RRT (OR 2,49 [95% CI 1,30-4,81], p= 0,006), and sepsis (OR 2,56 [95% CI 1,21-5,40], p= 0,014) as risk factors for mortality (Table 8). The model's Nagelkerke pseudo-R2 of 0,531 indicates a strong relationship between the predictors and mortality.

Discussion

This study provides a comprehensive analysis of drug-induced AKI in hospitalised cancer patients over two decades, highlighting evolving patterns in nephrotoxic agents, the growing need for HD, and associated mortality. Our findings align with global trends in oncology care, though they also reveal unique insights into the Portuguese oncological hospital setting.

To better grasp the several findings of this study, each topic will be addressed in the following subsections.

Evolution of drug-induced nephrotoxicity and changing drug profiles

Regarding the sample baseline characteristics, there was no significant difference in gender (p= 0,536) or cancer distribution (p= 0,906) between the two decades of the study, with only a slightly older sample in the second decade (median 59 [IQR 43-69] vs 62 [IQR 51-71] years old, p= 0,002).

There were significant differences, however, in the available/used treatments for these patients, either by the appearance of new drugs or by the change in incidence of AKI with classically known nephrotoxic drugs. There was a decrease in cases involving platinum-based drugs (10,2% vs 8,1%, p= 0,020) and an increase in cases involving a

combination of multiple drugs without cancer-directed therapy, mainly due to combinations of antibiotics, antivirals, or antifungals (17.5% vs 28.6%, p= 0.011). This trend may reflect advancements in cancer treatment protocols (e.g. intravenous hydration protocols), allowing for safer drug administrations with fewer adverse effects, particularly nephrotoxicity, for which clinicians are increasingly aware and able to treat. In fact, in a comprehensive cancer center, most AKI cases do not need a specialised nephrology evaluation and are managed by the oncology assistant team or referred to the nephrology outpatient clinic. Only a small proportion of AKI cases, usually KDIGO 2 or 3, need hospitalisation with follow-up by the nephrology team; those are the ones represented in this study (Figure 1). In addition, novel therapies like ICPI and TKI have become more prevalent, bringing new aspects to drug monitoring and side effects while allowing for less usage of classically known toxic chemotherapies. ICPIs and TKIs accounted for 4.8% and 1.5% of nephrotoxicity cases in the second decade, respectively, aligning with studies that report these agents' emerging role in inducing renal complications[4,7,8]. Kitchlu et al. reported similar findings, demonstrating an increase in AKI cases related to modern cancer therapies, particularly with the introduction of targeted therapies like TKI[15]. Our findings also resonate with the work of Perazella et al., which highlights the nephrotoxic potential of these new oncologic agents and underscores the necessity for vigilant renal monitoring in cancer patients receiving these treatments[18].

The nephrological profile identified in our population is similar to the outpatient nephrotoxic profile regarding cancer therapy as described in the study by Alonso et al.[19]. However, differences in the drug-induced nephrotoxicity profile were also identified since hospitalised patients, particularly those with critical illness or requiring intensive care, are exposed to a broader array of nephrotoxic agents beyond antineoplastic drugs, including antimicrobials and other supportive therapies. In fact, regardless of the decade

in analysis, cancer-directed therapy accounted for around one-fifth of the drug-induced AKI cases, with an overall percentage of 16,1% caused by a single nephrotoxic agent and 5,6% in combination with other nephrotoxic drugs. The most common nephrotoxic agents were NSAIDs and antibiotic drugs, with an overall representation of 19,3% and 15,9% as single nephrotoxic agents, respectively, also contributing to a large proportion of cases involving multiple drugs without cancer-directed therapy, making grossly one-quarter of all nephrotoxicity cases. These findings prove interest in showing that most cases of drug-induced AKI in a comprehensive cancer center are not caused by antineoplastic agents, highlighting the complexity of oncologic patients and the awareness for the surveillance of cancer treatments.

Haemodialysis and its increasing necessity

One of the significant findings of our study is the increase in the need for RRT over the two decades, rising from 25.5% to 36.6% (p= 0.024). This could reflect an increase in the complexity and severity of AKI cases, driven in part by the intensified use of nephrotoxic drug combinations and the longer survival of cancer patients. Patients with AKI who require RRT face significantly worse outcomes, including higher mortality rates, which is consistent with our findings, specifically in drug-induced AKI.

To begin, we ran a bivariate analysis, which showed several variables to be associated with a higher need for RRT, such as younger age, haematologic cancer, BMT, severe clinical complications like GVHD, IMV, and sepsis, and some drugs (antiviral, CNI, and the use of multiple drugs without cancer-directed therapy). On the other hand, most of the solid cancers, reversible clinical complications such as pre and post-renal AKI, and some drugs, particularly NSAID, platinum-based drugs, ICPI, and the use of multiple drugs with cancer-directed therapy, were associated with lower need for RRT. Although multivariate analysis cleared some of these predictors as confounding factors,

several thoughts can be made regarding this. Firstly, the need for RRT is higher when the measured factor implies greater severity of clinical status, such as haematologic cancers and several drugs. Interestingly, drugs other than antimicrobials and immunosuppressives do not seem to increase the need for RRT, as those are not expected to lead to irreversible AKI or bad prognosis; furthermore, there is tight surveillance over cancer therapy safety. Also noteworthy, younger patients had a higher need for RRT, which may be counterintuitive, although it may be explained by underlying oncologic disease profiles, such as a higher prevalence of haematologic cancer.

Notwithstanding, multivariate analysis summed up the predictors for the need for RRT to only three factors – haematologic cancer, IMV, and sepsis. Some of the predictors for the need for RRT, namely IMV and sepsis, are in line with other studies[5,20–24], which also identified these factors as strong indicators of severe AKI from all causes, requiring dialysis in critically ill general and cancer patients. Furthermore, we also found haematologic cancer as a risk factor for the need for RRT, which is generally associated with a worse prognosis than solid tumours. The practice of BMT, in some cases, leads to associated immunosuppression and risk of infectious diseases, prone to the need for nephrotoxic drugs such as several antimicrobials.

Mortality and AKI: a persistent challenge

The overall mortality rate in our cohort was high (29.5%), a finding that echoes the results of similar studies in cancer patients with AKI[25]. The need for RRT was a significant predictor of mortality, reinforcing the link between severe AKI and poor patient outcomes.

As was seen for the need for RRT (see above), grossly the same factors were predictors of higher or lower risk for mortality, also expressing relation to underlying

disease severity and treatment complications. Once more, no cancer therapy was associated with higher mortality.

Furthermore, multivariate analysis revealed that IMV, multiple nephrotoxic without cancer-directed therapy, RRT, and sepsis were the strongest predictors of death. Our findings are supported by other reports that found that cancer patients requiring RRT have markedly higher mortality rates than those with milder forms of AKI[2,26]. These authors also emphasised the impact of AKI on disrupting cancer treatment, contributing to disease progression and further worsening patient prognosis. This is consistent with the increased mortality observed in our cohort, where AKI likely interrupted cancer-directed therapy, reducing the effectiveness of cancer management. Nevertheless, prospective studies with follow-up after hospital discharge or studies addressing outpatient long-term implications of drug-induced AKI would better ascertain the causality nexus regarding worse clinical outcomes.

Clinical implications, future directions and research, strengths and weaknesses of the study

While the global trend toward more intensive cancer therapies has contributed to improved cancer survival, it has also resulted in increased rates of AKI and the need for interventions such as HD. Our study's findings emphasise the importance of balancing the oncological benefits of newer therapies with their potential for nephrotoxicity. The increase in AKI due to non-antineoplastic drugs, particularly antimicrobials, highlights the need for caution when prescribing these agents in the oncologic setting, especially in patients already at risk of renal impairment. Similar preventive measures like rigorous hydration protocols and dose adjustments for high-risk drugs like cisplatin to mitigate nephrotoxicity are suggested in various studies and recommendations. The use of nephroprotective agents, such as amifostine, has shown some promise in reducing

cisplatin-induced renal damage, though their use remains limited due to cost and side effects[9,27,28]. Notwithstanding, although this study showed many cases of drug-induced AKI due to cancer-directed therapy, it also showed that its effects seem to be reversible, without a strong association with the need for RRT or mortality and, in some cases, these drugs were associated to lower odds for these adverse events.

Our findings highlight the need for future research. The high mortality rates in patients requiring HD, particularly those with sepsis and IMV, suggest the need for more refined clinical tools to assess when dialysis should be initiated. The role of biomarkers in predicting AKI in cancer patients is also an area of growing interest. Biomarkers such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 have shown potential in identifying early kidney damage, allowing for timely interventions[29]. Incorporating these biomarkers into clinical practice could help oncologists and nephrologists to personalise treatment plans, balancing cancer efficacy with renal safety.

This is one of the few studies in the literature that gives an insight into drug-induced AKI in cancer patients, comprising a large sample of patients in an extended cohort. However, several limitations should be considered. First, the retrospective study design has inherent limitations, as evidenced by the large number of excluded cases and the lack of information regarding comorbidities and cancer status, particularly in the first decade of the cohort. Second, we did not account for heterogeneity in cancer stage and disease aggressiveness, which are relevant confounders when analysing predictors of RRT and mortality. That is also true for the ECOG scale and baseline chronic kidney disease, a known risk factor for AKI. Third, we did not analyse long-term mortality and chronic kidney disease development due to the lack of follow-up data, which would give greater insight into the implications of AKI in the oncologic therapy and outcome.

Conclusion

The evolution of drug-induced AKI in the oncologic setting over two decades demonstrates both the progress in cancer therapy and the challenges in managing renal complications in cancer care. As cancer treatments continue to evolve, research must focus on minimising the nephrotoxic effects of these therapies to improve overall patient outcomes and maintain the continuity of oncological care. When used correctly and with the necessary surveillance and prevention (i.e. hydration protocols and dose adjustments for high-risk drugs), the nephrotoxicity of cancer-directed therapy (such as platinum-based drugs, TKIs, or ICPI) is diluted among other nephrotoxic drug groups, common to oncologic and general hospitals. The increased use of HD and persistently high mortality rates underscore the need for better preventive strategies and closer collaboration between oncology and nephrology. Collaborative efforts between these specialities are critical to developing comprehensive care strategies that minimise kidney disease while maximising cancer treatment outcomes improving overall survival and quality of life.

Declaration of interest statement

The authors report that there are no competing interests to declare.

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Table 1: Demographics, clinical data, and outcomes in the first and second decades. AKI, acute kidney injury; GVHD, graft-versus-host disease; HD, haemodialysis; ICU, intensive care unit; IQR, interquartile range; N/A, not available; RRT, renal replacement therapy.

	First decade	Second decade	Overall	p
Demographic data				
Gender (n, %)				0,536
Male	82 (59,9)	172 (63,0)	254 (62,0)	
Female	55 (40,1)	101 (37,0)	156 (38,0)	
Age (median, IQR)				0,027*
	59 [43-69]	62 [51-71]	61 [48-71]	
Age group (n, %)				0,002*
0-9	8 (5,8)	1 (0,4)	9 (2,2)	
10-19	4 (2,9)	11 (4,0)	15 (3,7)	
20-29	2 (1,5)	12 (4,4)	14 (3,4)	
30-39	12 (8,8)	11 (4,0)	23 (3,6)	
40-49	19 (13,9)	27 (9,9)	46 (11,2)	
50-59	28 (20,4)	54 (19,9)	82 (20,0)	
60-69	35 (25,5)	68 (25,0)	103 (25,2)	
70-79	20 (14,6)	69 (25,4)	89 (21,8)	
80-89	7 (5,1)	18 (6,6)	25 (6,1)	
90-99	2 (1,5)	1 (0,4)	3 (0,7)	
Oncologic data				
Cancer group (n, %)				0,906
Breast	8 (5,8)	9 (3,3)	17 (4,1)	
Gastrointestinal	22 (16,1)	51 (18,7)	73 (17,8)	
Gynecologic	7 (5,1)	12 (4,4)	19 (4,6)	
Head and neck	12 (8,8)	18 (6,6)	30 (7,3)	
Haematologic	60 (43,8)	118 (43,2)	178 (43,4)	
Lung	6 (4,4)	14 (5,1)	20 (4,9)	
Sarcoma	6 (4,4)	9 (3,3)	15 (3,7)	
Skin	2 (1,5)	6 (2,2)	8 (2,0)	
Urologic	12 (8,8)	30 (11,0)	42 (10,2)	
Others	2 (1,5)	6 (2,2)	8 (2,0)	
>1 cancer (n, %)				N/A
Yes	N/A	12 (0,5)	12 (0,5)	
No	N/A	398 (99,5)	398 (99,5)	
Haematological transplant (n, %)				
Bone marrow transplant	33 (24,1)	56 (20,5)	89 (21,7)	0,408
of which autologous transplant	25 (18,3)	25 (9,2)	50 (12,2)	0,004*
of which allogeneic transplant	8 (5,8)	31 (11,3)	39 (9,5)	0,004*
AKI related data				
AKI associated conditions (n, %)				
Concomitant pre-renal AKI	5 (3,6)	25 (9,2)	39 (9,5)	0,043*
Concomitant post-renal AKI	14 (10,2)	20 (7,3)	34 (8,3)	0,316
Glomerulonephritis	0 (0)	1 (0,4%)	1 (0,2)	N/A
Graft-versus-host disease	11 (8,0)	24 (8,8)	35 (8,5)	0,795
Hypercalcemia	3 (2,2)	11 (4,0)	14 (3,4)	0,333
Post-operatory status	8 (5,8)	12 (4,4)	20 (4,9)	0,522
Sepsis	37 (27,0)	105 (38,5)	142 (34,6)	0,021*
Thrombotic microangiopathy	4 (2,9)	6 (2,2)	10 (2,4)	0,655
Tumor lysis syndrome	2 (1,5)	13 (4,8)	15 (3,7)	0,093
Tumoral infiltration	11 (8,0)	24 (8,8)	7 (1,7)	0,059
Clinical outcomes				
RRT (n, %)				
RRT	35 (25,5)	100 (36,6)	135 (32,9)	0,024*
of which continuous HD	22 (16,1)	59 (21,6)	81 (19,8)	0,183
of which intermittent HD	17 (12,4)	54 (19,8)	71 (17,3)	0,052
ICU and Mortality (n, %)				
Invasive mechanical ventilation	33 (24,1)	71 (26,0)	104 (25,4)	0,673
Deaths	34 (24,8)	87 (31,9)	121 (29,5)	0,140

Table 2: Nephrotoxic drug group implicated in acute kidney injury per case (n= 410). Note: When several drug groups were involved, they are referred to as 'Multiple' and subdivided into groups' with' or 'without' anti-cancer therapy. N/A, not available; RAASi, renin-angiotensin-aldosterone system inhibitor.

	First decade	Second decade	Overall	p
Number of nephrotoxic drugs per patient (distribution; median, IQR)	1 [1-2]	1 [1-2]	1 [1-2]	0,061
Number of nephrotoxic drugs per patient (frequencies; n,%)				0,295
1	97 (70,8)	173 (63,4)	270 (65,9)	
2	23 (16,8)	39 (14,3)	62 (15,1)	
3	11 (8,0)	36 (13,2)	47 (11,5)	
4	3 (2,2)	15 (5,5)	18 (4,4)	
5	2 (1,5)	7 (2,6)	9 (2,2)	
6	1 (0,7)	1 (0,4)	2 (0,5)	
7	0 (0)	2 (0,7)	2 (0,5)	
Nephrotoxic drug group (n, %)				
Antibiotic	27 (19,3)	38 (13,9)	65 (15,9)	0,077
Antifungal	2 (1,5)	2 (0,7)	4 (1,0)	0,480
Antiviral	7 (5,1)	8 (2,9)	15 (3,7)	0,276
Bisphosphonate	0 (0)	6 (2,2)	6 (1,5)	N/A
Calcineurin inhibitor	8 (5,8)	6 (2,2)	14 (3,4)	0,055
Immune checkpoint inhibitor	0 (0)	13 (4,8)	13 (3,2)	N/A
Iodinated contrast	13 (9,5)	17 (6,2)	30 (7,3)	0,232
Non-steroidal anti-inflammatory	26 (19,0)	53 (19,4)	79 (19,3)	0,916
Other chemotherapies	4 (2,9)	9 (3,3)	13 (3,2)	0,837
Platinum-based chemotherapy	14 (10,2)	22 (8,1)	36 (8,8)	0,020*
RAASi	2 (1,5)	0 (0)	2 (0,5)	N/A
Tyrosine kinase inhibitor	0 (0)	4 (1,5)	4 (1,0)	N/A
Others	1 (0,7)	3 (1,1)	4 (1,0)	0,720
Multiple (with anti-cancer therapy)	9 (6,6)	14 (5,1)	23 (5,6)	0,550
Multiple (without anti-cancer therapy)	24 (17,5)	78 (28,6)	102 (24,9)	0,011*
Total	137 (100)	273 (100)	410 (100)	

Table 3: Bivariate analysis assessing risk factors for the need for RRT. AKI, acute kidney injury; CI, confidence interval; N/A, not available; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy.

Factors	**Need for RRT** [n (%)] If factor present	If factor not present	**Odds ratio (CI)**	**p**
Demographic data				
Gender				
Male	81 (31,9)	54 (34,6)	0,88 (0,58-1,35)	0,569
Oncologic data				
Cancer group				
Breast	0 (0)	135 (34,4)	N/A	0,003*
Gastrointestinal	13 (17,8)	122 (36,2)	0,38 (0,20-0,72)	0,002*
Gynaecologic	1 (5,3)	134 (34,3)	0,11 (0,01-0,91)	0,009*
Head and neck	2 (6,7)	133 (35,0)	0,13 (0,03-0,57)	0,001*
Haematologic	105 (59,0)	30 (12,9)	9,69 (5,96-15,75)	<0,001*
Lung	2 (10,0)	133 (34,1)	0,22 (0,05-0,94)	0,025*
Sarcoma	3 (20,0)	132 (33,4)	0,50 (0,14-1,77)	0,278
Skin	1 (12,5)	134 (33,3)	0,29 (0,04-2,35)	0,214
Urologic	7 (16,7)	128 (34,8)	0,36 (0,16-0,87)	0,018*
Others	1 (12,5)	134 (33,3)	0,29 (0,04-2,35)	0,214
Number of cancers				
>1 cancer	4 (33,3)	131 (32,9)	1,02 (0,30-3,45)	0,976
Haematological transplant				
Bone marrow transplant	61 (68,5)	74 (23,1)	7,27 (4,34-12,20)	<0,001*
AKI related data				
AKI associated conditions				
Concomitant pre-renal AKI	2 (6,7)	133 (35,0)	0,13 (0,03-0,57)	0,001*
Concomitant post-renal AKI	6 (17,6)	129 (34,3)	0,41 (0,17-1,02)	0,048*
Glomerulonephritis	0 (0)	135 (33,0)	N/A	0,483
Graft-versus-host disease	25 (71,4)	110 (29,3)	6,02 (2,80-12,96)	<0,001*
Hypercalcemia	3 (21,4)	132 (33,3)	0,55 (0,15-1,99)	0,352
Post-operatory status	2 (10,0)	133 (34,1)	0,22 (0,05-0,94)	0,025*
Sepsis	94 (66,2)	41 (15,3)	10,84 (6,70-17,54)	<0,001*
Thrombotic microangiopathy	5 (50,0)	130 (32,5)	2,08 (0,59-7,30)	0,245
Tumour lysis syndrome	8 (53,3)	127 (32,2)	2,41 (0,86-6,80)	0,087
Tumoral infiltration	3 (42,9)	132 (32,8)	1,54 (0,34-6,98)	0,573
Nephrotoxic drug-related data				
Nephrotoxic drug group				
Antibiotic	21 (32,3)	114 (33,0)	0,97 (0,55-1,70)	0,908
Antifungal	1 (25,0)	134 (33,0)	0,68 (0,07-6,57)	0,735
Antiviral	10 (66,7)	125 (31,6)	4,07 (1,45-12,90)	0,005*
Bisphosphonate	2 (33,3)	133 (32,9)	1,02 (0,18-5,63)	0,983
Calcineurin inhibitor	9 (64,3)	126 (31,8)	3,86 (1,27-11,75)	0,011*
Immune checkpoint inhibitor	1 (7,7)	134 (33,8)	0,16 (0,2-1,27)	0,049*
Iodinated contrast	8 (26,7)	127 (33,4)	0,72 (0,31-1,67)	0,449
Non-steroidal anti-inflammatory	7 (8,9)	128 (38,7)	0,15 (0,07-0,35)	<0,001*
Other chemotherapies	2 (15,4)	133 (33,5)	0,36 (0,08-1,65)	0,171
Platinum-based chemotherapy	5 (13,9)	130 (34,8)	0,30 (0,12-0,80)	0,011*
RAASi	0 (0)	135 (33,1)	N/A	0,321
Tyrosine kinase inhibitor	1 (25,0)	134 (33,0)	0,68 (0,07-6,57)	0,735
Others	1 (25,0)	134 (33,0)	0,68 (0,07-6,57)	0,735
Multiple (with anti-cancer therapy)	3 (13,0)	132 (34,1)	0,29 (0,09-0,99)	0,037*
Multiple (without anti-cancer therapy)	61 (62,0)	73 (23,5)	5,30 (3,27-8,57)	<0,001*
Clinical outcomes				
Intensive care unit				
Invasive mechanical ventilation	85 (81,7)	50 (16,3)	22,9 (12,8-41,0)	<0,001*

Table 4: Multivariate analysis assessing risk for the need for renal replacement therapy within the drug groups implicated. CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

Factors	B coefficient	Standard error	Odds ratio (CI)	p
Antibiotic	0,712	0,343	2,038 (1,040-3,993)	0,038
Antiviral	2,145	0,589	8,538 (2,689-27,110)	<0,001
Calcineurin inhibitor	2,039	0,599	7,685 (2,376-24,851)	<0,001
NSAID	-0,879	0,452	0,415 (0,171-1,006)	0,052
Multiple (without anti-cancer therapy)	1,941	0,300	6,966 (3,870-12,537)	<0,001
Constant	-4,506	1,281	0,011	<0,001

Table 5: Multivariate analysis assessing risk for the need for renal replacement therapy within all the variables in the study. CI, confidence interval.

Factors	B coefficient	Standard error	Odds ratio (CI)	p
Haematologic cancer	1,159	0,300	3,188 (1,772-5,735)	<0,001
Sepsis	0,773	0,359	2,166 (1,073-4,376)	0,031
Invasive mechanical ventilation	1,923	0,408	6,842 (3,076-15,217)	<0,001
Constant	-2,447	0,466	0,087	<0,001

Table 6: Bivariate analysis assessing risk factors for mortality. AKI, acute kidney injury; CI, confidence interval; N/A, not available; RAASi, renin-angiotensin-aldosterone system inhibitor.

Factors	**Mortality** [n (%)] If factor present	If factor not present	**Odds ratio (CI)**	**p**
Demographic data				
Gender				
Male	78 (30,7)	43 (27,6)	1,16 (0,88-1,81)	0,498
Oncologic data				
Cancer group				
Breast	0 (0)	121 (30,8)	N/A	0,006*
Gastrointestinal	9 (12,3)	112 (33,2)	0,28 (0,14-0,59)	<0,001*
Gynaecologic	0 (0)	121 (30,9)	N/A	0,004*
Head and neck	2 (6,7)	119 (31,3)	0,16 (0,04-0,67)	0,004*
Haematologic	96 (53,9)	25 (10,8)	9,69 (5,83-16,13)	<0,001*
Lung	4 (20,0)	117 (30,0)	0,58 (0,19-1,78)	0,339
Sarcoma	3 (20,0)	118 (29,9)	0,59 (0,16-2,12)	0,411
Skin	1 (12,5)	120 (29,9)	0,34 (0,04-2,76)	0,287
Urologic	6 (14,3)	115 (31,3)	0,37 (0,15-0,90)	0,022*
Others	0 (0)	121 (30,1)	N/A	0,065
Number of cancers				
>1 cancer	5 (41,7)	116 (29,1)	1,74 (0,54-5,59)	0,349
Haematological transplant				
Bone marrow transplant	57 (64,0)	64 (19,9)	7,15 (4,29-11,94)	<0,001*
AKI related data				
AKI associated conditions				
Concomitant pre-renal AKI	4 (13,3)	117 (30,8)	0,35 (0,12-1,01)	0,044*
Concomitant post-renal AKI	6 (17,6)	115 (30,6)	0,49 (0,20-1,21)	0,113
Glomerulonephritis	0 (0)	121 (29,6)	N/A	0,517
Graft-versus-host disease	21 (60,0)	100 (26,7)	4,13 (2,02-8,42)	<0,001*
Hypercalcemia	4 (28,6)	117 (29,5)	0,95 (0,29-3,10)	0,937
Post-operatory status	3 (15,0)	118 (30,3)	0,41 (0,12-1,41)	0,145
Sepsis	91 (64,1)	30 (11,2)	14,16 (8,49-23,61)	<0,001*
Thrombotic microangiopathy	4 (40,0)	117 (29,3)	1,61 (0,45-5,82)	0,462
Tumour lysis syndrome	8 (53,3)	113 (28,6)	2,85 (1,01-8,05)	0,039*
Tumoral infiltration	3 (42,9)	118 (29,3)	1,81 (0,39-8,22)	0,435
Nephrotoxic drug-related data				
Nephrotoxic drug group				
Antibiotic	11 (16,9)	110 (31,9)	0,44 (0,22-0,87)	0,015*
Antifungal	1 (25,0)	134 (33,0)	0,68 (0,07-6,57)	0,735
Antiviral	8 (53,3)	113 (28,6)	2,85 (1,01-8,05)	0,039*
Bisphosphonate	1 (16,7)	120 (29,7)	0,47 (0,06-4,10)	0,487
Calcineurin inhibitor	7 (50,0)	114 (28,8)	2,47 (0,85-7,21)	0,087
Immune checkpoint inhibitor	1 (7,7)	120 (30,2)	0,19 (0,3-1,50)	0,080
Iodinated contrast	3 (10,0)	118 (31,1)	0,25 (0,07-0,83)	0,015*
Non-steroidal anti-inflammatory	7 (8,9)	114 (34,4)	0,19 (0,08-0,42)	<0,001*
Other chemotherapies	3 (23,1)	118 (29,7)	0,71 (0,19-2,62)	0,171
Platinum-based chemotherapy	4 (11,1)	117 (31,3)	0,28 (0,10-0,79)	0,011*
RAASi	0 (0)	121 (29,7)	N/A	0,359
Tyrosine kinase inhibitor	0 (0)	121 (29,8)	N/A	0,193
Others	2 (50,0)	119 (29,3)	2,41 (0,34-17,32)	0,367
Multiple (with anti-cancer therapy)	3 (13,0)	118 (30,5)	0,34 (0,10-1,17)	0,075
Multiple (without anti-cancer therapy)	67 (67,0)	54 (17,4)	9,63 (5,78-16,03)	<0,001*
Clinical outcomes				
Renal replacement therapy				
Renal replacement therapy	83 (61,5)	38 (13,8)	9,96 (6,12-16,21)	<0,001*
of which continuous hemodialysis	54 (66,7)	67 (20,4)	7,82 (4,58-13,34)	<0,001*
of which intermittent hemodialysis	41 (56,9)	80 (23,7)	4,27 (2,51-7,24)	<0,001*
Intensive care unit				
Invasive mechanical ventilation	83 (79,8)	38 (12,4)	27,9 (15,5-50,1)	<0,001*

Table 7: Multivariate analysis assessing risk for mortality within the drug groups implicated. CI, confidence interval.

Factors	B coefficient	Standard error	Odds ratio (CI)	p
Antifungal	3,000	1,168	20,083 (2,034-198,343)	0,010
Antiviral	2,035	0,548	7,651 (2,616-22,375)	<0,001
Calcineurin inhibitor	1,901	0,564	6,694 (2,218-20,205)	<0,001
Multiple (without anti-cancer therapy)	2,609	0,278	13,592 (7,886-23,427)	<0,001
Constant	-7,644	1,490	0,000	<0,001

Table 8: Multivariate analysis assessing risk for mortality within all the variables in the study. CI, confidence interval

Factors	B coefficient	Standard error	Odds ratio (CI)	p
Invasive mechanical ventilation	1,178	0,332	3,247 (1,694-6,222)	<0,001
Multiple (without anti-cancer therapy)	1,941	0,300	6,966 (3,870-12,537)	<0,001
Renal replacement therapy	0,914	0,335	2,494 (1,295-4,805)	0,006
Sepsis	0,938	0,382	2,555 (1,209-5,400)	0,014
Constant	-3,092	0,521	0,045	<0,001

Figure 1: Follow-up of AKI cancer patients in a comprehensive cancer center. AKI, acute kidney injury.