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Acute Kidney Injury in Critically Ill Patients with Hematological Malignancies Significantly Worsens Long-Term Mortality and Morbidity. Results of An 8-year Retrospective Cohort with Long-Term Follow-Up

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Abstract

Background: Short-term outcomes of critically ill patients with hematological malignancies (HM) who developed acute kidney injury (AKI) is grim. Little is known about their long-term management. We aimed to assess the impact of the occurrence of AKI on long-term outcome and management in those patients.

Methods: We conducted a single-center retrospective study in a tertiary-care French intensive care unit (ICU) with HM patients admitted between January 1, 2012 and December 31, 2020. The primary outcome was 3-year mortality.

Results: A cohort of 353 patients was analyzed, median age 62 (52; 69) years, 65% male, median SAPS II score 51 (41, 62) and sequential organ failure assessment score 6 (4; 9). AKI occurred in 67.7% of patients, with 26% at stage 1, 24.8% at stage 2 and 49.2% at stage 3 of the KDIGO classification. Three-year mortality was 77.2% in the overall population, with a significantly higher rate in patients who developed AKI (81.9% *versus* 66.7%, p<0.01). Recovery or maintenance of previous renal function was 86.8% in surviving patients without AKI and 69.9% in those with AKI (p<0.01). Among patients who developed AKI, 59.9% were able to continue their hematological treatment program, compared with 73% for the others (p=0.03).

Conclusions: AKI affects two-thirds of HM patients admitted to intensive care, with a significant impact on three-year mortality. Most patients who survive recover their previous renal function, and the occurrence of AKI does not substantially alter the subsequent treatment regimen. These results should encourage intensivists not to limit the management of these patients.

Keywords: Acute kidney injury; Hematological malignancy; ICU; long term outcome; prognosis

List of abbreviations: AKI: acute kidney failure; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ARF: acute respiratory failure; CAR-T: chimeric antigen receptor-T; CKD: chronic kidney disease; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; H-LOShospital length of stay; HL: Hodgkin's lymphoma; HM: hematological malignancy; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; ICU-LOSintensive care unit length of stay; IQR: interquartile range; IRB: institutional review board; ISN: International Society of Nephrology; KDIGO: Kidney Disease : Improving Global Outcomes; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPL: myeloproliferative syndrome; NHL: non-Hodgkin's lymphoma; OR: odds ratio; OS: overall survival; PS: performance status; RFS: relapse-free survival; RRT: renal replacement therapy; SAPS II: simplified acute physiology score II; SD: standard deviation; SOFA: sequential organ failure assessment; SSC: Survival Sepsis Campaign

Introduction

Hematological malignancies (HM) represent 12% of newly-diagnosed cancer cases [1]. During their course, 15 to 22% of these patients will be admitted to the intensive care unit (ICU) [2, 3]. Their prognosis has improved considerably over the last decades, resulting in a significant decrease in mortality. Several factors contribute to this improvement: the development of supportive care and novel curative therapies, earlier admission and better selection of patients who could benefit from their admission [4–7]. The occurrence of organ failures is a well-known poor prognostic factor that has a significant impact on the survival and on the long term outcome of these patients [8, 9].

Acute kidney injury (AKI) is common in the ICU, representing 20 to 40% of the general critical care population [10–12]. It is associated with a significant increase in mortality, length of stay and hospitalization costs, as well as higher cardiovascular morbidity and impact on subsequent renal function [10, 11, 13–15].

Patients with HM are particularly prone to develop AKI. An increased susceptibility to shock, sepsis or the occurrence of specific complications such as tumor lysis syndrome or chemotherapy toxicity can expose up to 75% of these patients to this condition [16–23]. In 2013, a prospective study including 200 patients showed that 69% had developed AKI according to RIFLE criteria [18]. Of the patients with AKI, more than half required an RRT. A few years later, a larger multicenter study including 1009 patients confirmed the high incidence of AKI in this population [19]. Two-thirds of these patients had AKI, regardless of AKIN stage, during their ICU stay. Nearly 40% of these patients underwent RRT, with a consequent increase in mortality rates.

Mortality rates as high as 88% have been described in the most severe cases of AKI requiring renal replacement therapy (RRT) in allogeneic hematopoietic stem cell transplantation (HSCT) patients [24]. The development of AKI and its possible perpetuation may also limit the use of chemotherapy or increase its toxicity and thus potentially modify the disease course [16–18, 23, 25]. However, most of these data come from studies dating back several years. In the more recent studies, heterogeneities in patient selection and in the different used definitions prevent any generalization of these results [17, 26, 27]. In addition, long-term outcome of the ICU survivors have never been described to our knowledge.

We designed this study to assess the impact of the occurrence of AKI on the long-term prognosis, and management in critically ill patients with HM.

Material and Methods

Study Design

This retrospective study was carried out in the Medical ICU of Lapeyronie University Hospital (Montpellier, France). The ethics committee from the institutional review board (IRB) of the Montpellier University Hospital approved the study (approval number: IRB-MTP_2022_04_202201037) and waived the need for informed consent. No data allowing patient identification were collected. Clinical investigations were conducted in accordance with both French law and the Declaration of Helsinki.

Our 20-bed intensive care unit admits around 900 patients a year, a third of whom come from the hematology department located in the Saint-Eloi University Hospital (Montpellier, France). Patients suffering from all types of HM are transferred to our intensive care unit when they present a serious and life-threatening condition, and are monitored concomitantly by the hematology and intensive care teams. The decision to admit these patients to intensive care and to treat them intensively must be made by both intensivists and hematologists, and according to the wishes of the patient and his or her family. Intensivists and hematologists are available 24 hours a day, 7 days a week.

Patients

We included all patients over 18 years of age consecutively admitted to our ICU between January 1, 2012 and December 31, 2020, with HM associated with a severe complication. Patients with stage IV and V chronic kidney disease (CKD) were excluded from our analysis because of their greater propensity to require RRT. Patients who objected to their data collection were also excluded from the study.

Clinical and biological data were collected retrospectively after extraction from patients' electronic medical records, then recorded anonymously in a spreadsheet. They included patient demographics, such as age, gender, comorbidities, particularly renal history, and performance status (PS) [28]. The main characteristics of the hemopathy were also collected, such as its type, date of diagnosis, status (newly diagnosed, partial response, complete response or refractory/relapsing) and the time elapsed between diagnosis and admission to the ICU. Each HM was classified as myeloid: acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia and myeloproliferative syndrome; lymphoid: acute lymphoblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma and chronic lymphocytic leukemia; and multiple myeloma.

On admission to the ICU, time since hospitalization and since HM diagnosis were collected, as well as severity scores: Simplified Acute Physiology Score 2 (SAPS II) [29] and Sequential Organ Failure Assessment (SOFA) [30]. During the ICU stay, the occurrence and duration of organ failures were collected, as well as the required supportive therapies. We recorded the onset and severity of AKI for each patient, both on admission and during their stay in ICU. AKI was defined according to Kidney Disease: Improving Global Outcome (KDIGO) 2012 recommendations [26], as an increase in blood creatinine of at least 26.5 μmol/L over 48 hours, or 50% above baseline, and/or the occurrence of oliguria of less than 0.5 mL/kg/hour for 6 hours. Its severity was then graded according to KDIGO stages. Baseline creatinine level was defined as the lowest found 3 months prior to ICU admission. The use of RRT was recorded, including the time elapsed from the onset of AKI to its initiation, duration and eventual withdrawal. Renal recovery was defined as being alive, weaned from the RRT and having a creatinine level less than 25% higher than that prior to admission to the ICU [31]. CKD was defined as a glomerular filtration rate lower than 60 mL/min/1.73m^2 for more than 3 months [26].

ICU and hospital mortalities and respective lengths of stay were assessed. After hospital discharge, surviving patients were followed for at least 3 years and mortality at one and 3 years was assessed. Overall survival (OS) was defined as the time elapsed from ICU admission to the date of death from any cause. Plasma creatinine and creatinine clearance were recorded at 3, 6 and 12 months.

During follow-up, we checked whether the planned chemotherapy had been administered, the status of the HM, the occurrence of a relapse and its possible treatment. Status was assessed by the hematology team, and considered refractory when HM remained progressive during treatment, and relapsed when it progressed after the end of treatment. Relapse-free survival (RFS) was defined as the time between ICU admission to the date of the first hematological event: progression, relapse or all-cause death. Follow-up duration was as long as possible, with a primary endpoint assessment at three years.

Statistical Analysis

A Kolmogorov-Smirnov test was used to confirm the normality of the distribution for continuous variables. Categorical variables were reported with the number of observations (n) and the frequency of each modality (%) and compared using the Chi-2 test or Fisher's exact test (if appropriate). Quantitative variables were reported with the usual statistics: mean and standard deviation (SD) and median and range (min-max) and compared using the Wilcoxon test.

Median follow-up was calculated using Schemper method. RFS and OS were estimated using the Kaplan Meier method and compared using the Log-rank test. Multivariate analyses were performed using the Cox proportional hazards model (the *p*-value of the likelihood ratio test was reported). Variables with univariate *p*-values <0.15 were selected for multivariate analysis and a backward covariate selection was performed. Hazard ratios were reported with 95% confidence interval (CI).

All statistical tests were two-tailed and *p*-values <0.05 were considered statistically significant. All statistical analyses were performed with the STATA 16 software (StatCorp, College Station, TX).

For the main analysis, two groups of patients were distinguished according to the occurrence of AKI during their stay in intensive care: without AKI and with AKI. Three subgroups were identified in the cohort according to the severity of renal failure: patients without AKI, patients with AKI not requiring RRT and patients requiring RRT.

The primary objective was 3-year mortality according to the occurrence of AKI. Secondary objectives were the impact of the occurrence of AKI on subsequent treatment of hematological disease in patients surviving the ICU stay.

Results

Population and Characteristics

During the study period, 406 patients were deemed eligible, 353 of whom were included in our cohort (Figure 1). One hundred and twenty four females and 229 males (65%) with a median age of 62 (52–69) years were then studied. Their baseline characteristics are summarized in Table 1.

Prior health status of our population was fair since 57.5% of PS were <2. Almost half of the patients were being treated for lymphoid hemopathy (49.6%), over a third for myeloid hemopathy (36.5%) and 13.9% for multiple myeloma. On ICU admission, 117 patients (33.2%) had a newly-diagnosed HM and 123 (34.8%) had relapsed or refractory HM. Patients were admitted mainly for acute respiratory failure (143, 40.5%), or shock (126, 35.7%), less frequently for renal or metabolic disorders (48, 13.6%). The high median SAPS II and SOFA scores at ICU admission, 51 (41–62) and 6 (4–9) respectively, underlined the severity of the patients' illnesses (Table 2). Vasopressors were required in 201 patients (57.1%), invasive mechanical ventilation in 120

(34%), and RRT in 95 (26.9%) (Table 2). Median ICU and hospital length-of-stay were 5 (3–11) and 31 (18–52) days respectively (Table 2). The ICU mortality rate was 28.9%. A further 45 patients died before hospital discharge bringing in-hospital mortality rate to 41.6%.

Thus, 206 (58.3%) patients were discharged alive from the hospital and included in our long-term analysis (Figure 1). Patients were followed for a median period of 4.3 (95% CI [3.7–5.4]) years from ICU admission, with a median overall survival of 0.3 (95% CI [0.21–0.44]) years. Around two-thirds of patients died within a year of admission to the ICU, with most of the remainder staying alive thereafter (Figure 2). After hospital discharge, initial hematological chemotherapy was maintained in 164/206 surviving patients (79.6%), with nearly 2/3 of all surviving patients (127/206, 61.6%) being refractory or relapsed. Median relapse-free survival was 4 (CI 95% [3.2–7.1]) months (Table 3, Supplementary Figure 1).

Table 1: Patient characteristics at baseline

Characteristics at baseline	Total (N=353)	No AKI (N=114)	AKI (N=239)	p
Age, years, median (IQR)	62 (52–69)	61 (49–70)	63 (55–69)	0.15
Gender, male, n (%)	229 (64.9)	67 (58.8)	162 (67.8)	0.10
Performance status, n (%)				0.07
0–1	202 (57.2)	81 (40.1)	121 (59.9)	
2–4	151 (42.8)	40 (26.5)	111 (73.5)	
Chronic kidney disease, n (%)	44 (12.6)	5 (4.4)	39 (16.7)	<0.01
Hematologic malignancies, n (%)				
Lymphoid (HL, NHL, ALL and CLL)	175 (49.6)	66 (57.9)	109 (45.6)	
Myeloid (AML, MDS, CML and MPS)	129 (36.5)	37 (32.5)	92 (38.5)	
Multiple myeloma	49 (13.9)	11 (9.6)	38 (15.9)	
Delay from diagnosis to ICU admission, days, median (IQR)				
Onset of hospitalization	9 (1–20)	10.5 (2–22)	9 (1–19)	0.33
Onset of HM	286 (51–919)	213.5 (44–693)	341 (61–1090)	0.10
HM status at ICU admission, n (%)				0.33
Newly–diagnosed	117 (33.2)	42 (36.9)	75 (31.4)	
Refractory/relapsing	123 (34.8)	34 (29.8)	89 (37.2)	
Complete response	87 (24.6)	27 (23.7)	60 (25.1)	
Partial response	26 (7.4)	11 (9.6)	15 (6.3)	

AKI: acute kidney injury; IQR: interquartile range; HL: Hodgkin's lymphoma; NHL: non-Hodgkin's lymphoma; ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; AML: acute myeloid leukemia; MDS; myelodysplastic syndrome; CML; chronic myeloid leukemia; MPS: myeloproliferative syndrome; HM: hematological malignancies; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; ICU: intensive care unit.

Table 2: Patient characteristics at ICU admission

Characteristics at ICU admission	Total (N=353)	No AKI (N=114)	AKI (N=239)	p[a]	AKI–no RRT (N=144)	AKI–RRT (N=95)	p[b]
SAPS II, median (IQR)	51 (41–62)	45 (37–55)	56 (44–67)	<0.01	52.5 (41–62)	60 (48–82)	<0.01
SOFA score, median (IQR)	6 (4–9)	5 (3–7)	7 (5–10)	<0.01	6 (4–8)	10 (7–12)	<0.01
Non–renal SOFA score, median (IQR)	6 (3–8)	4 (3–7)	6 (4–9)	<0.01	5 (3–8)	8 (5–10)	<0.01
Vasopressors							
N (%)	201 (57.1)	45 (39.5)	156 (65.5)	<0.01	81 (56.6)	75 (79)	<0.01
Duration, days, median (IQR)	4 (2–7)	3 (2–5)	4 (2–9)	0.03	3 (2–5)	6 (3–13.5)	<0.01
Invasive mechanical ventilation							
N (%)	120 (34)	21 (18.4)	99 (41.4)	<0.01	37 (25.7)	62 (65.3)	<0.01
Duration, days, median (IQR)	6 (3–14)	6 (3–11)	5 (3–15)	0.79	5 (3–11)	7 (3–19)	0.65
Renal replacement therapy							
N (%)	95 (26.9)		95 (39.8)				
Duration, days, median (IQR)	5 (2–10)		5 (2–10)				
ICU–LOS, days, median, (IQR)	5 (3–11)	5 (3–9)	6 (3–12)	0.08	4 (3–8)	10 (5–19)	<0.01
H–LOS, days, median (IQR)	31 (18–52)	34 (20–52)	29 (17–54)	0.26	27.5 (16–48.5)	33 (19–60)	0.18
Mortality, N (%)							
ICU	102 (28.9)	10 (8.8)	92 (38.5)	<0.01	35 (24.3)	57 (60)	<0.01
Hospital	147 (41.6)	24 (21.1)	123 (51.5)	<0.01	56 (38.9)	67 (70.5)	<0.01

AKI: acute kidney injury; IQR: interquartile range; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; ICU: intensive care unit; LOS: length of stay; H: hospital. p[a]: no AKI vs AKI; p[b]: no AKI vs AKI-no RRT vs AKI-RRT.

Table 3: Follow–up of the entire cohort according to the occurrence of AKI

Follow–up parameters	Total (N=206)	No AKI (N=90)	AKI (N=116)	p
Creatinine levels, µmol/L (IQR)				
At ICU discharge	81 (55–121.5)	58 (46–72)	106.5 (69–162)	<0.01
3 months from ICU discharge	71.5 (57–94.5)	64 (54–73)	82.5 (63–112)	<0.01
6 months from ICU discharge	73 (59.5–98)	69 (56–77)	81 (65–119)	<0.01
12 months from ICU discharge	72.5 (61.5–99.5)	69 (59–76)	86 (66–119)	<0.01
Pursuit of hematological plan, N (%)	164 (79.6)	76 (84.4)	88 (75.9)	0.03
R/R after ICU discharge				
N (%)	127 (61.6)	47 (52.2)	80 (68.9)	0.15
Time to event, days, median (IQR)	41 (10–146)	41 (17–138)	38 (7–147)	0.48

AKI: acute kidney injury; IQR: interquartile range; ICU: intensive care unit; R/R: refractory or relapsing.

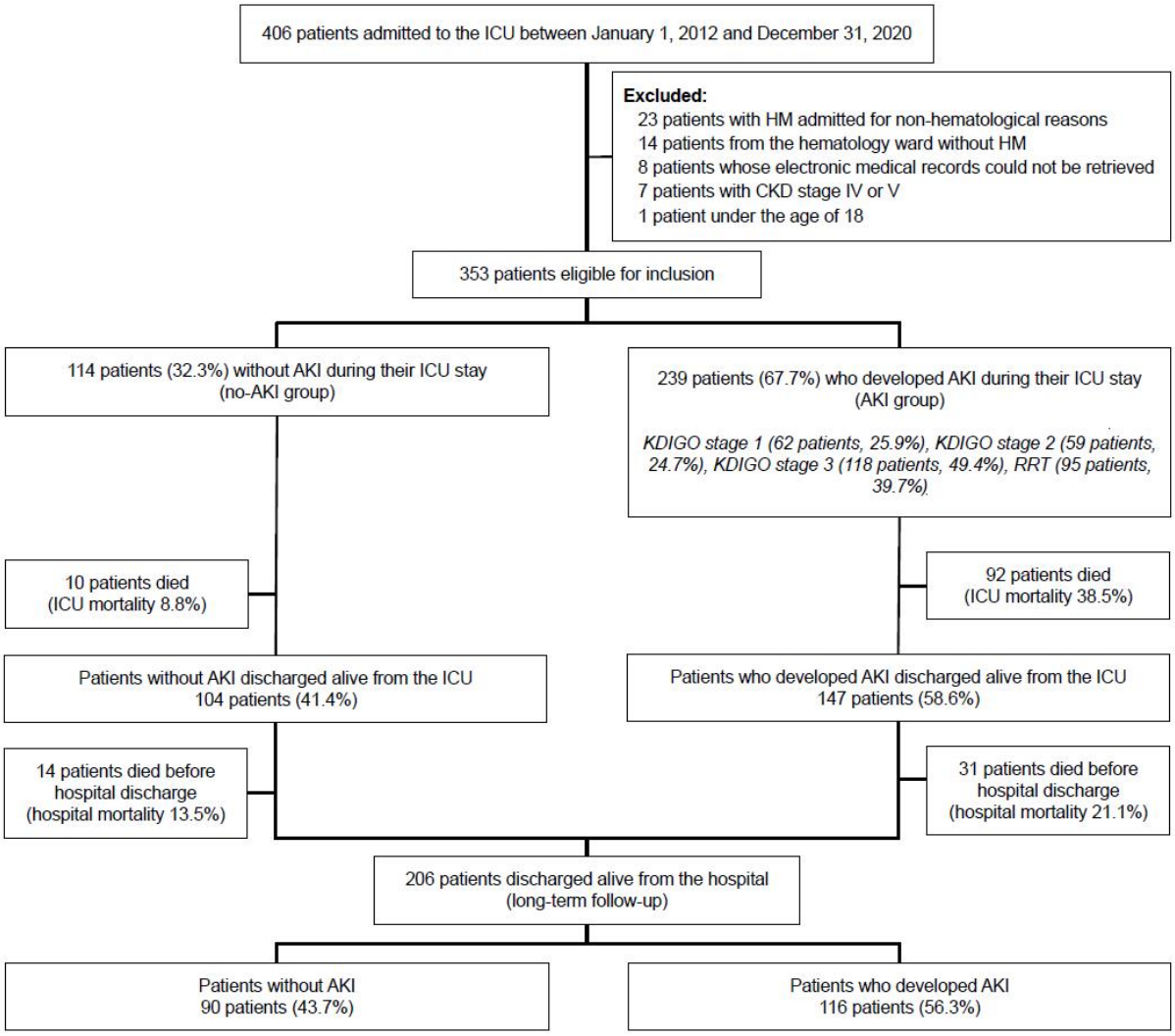


Figure 1 : Flow chart of the studied population

ICU: Intensive Care Unit; HM: hematological malignancies; CKD: chronic kidney disease; AKI: acute kidney injury; KDIGO: Kidney Disease Improving Global Outcome; RRT: renal replacement therapy.

Incidence, prognosis of AKI and impact on long-term outcome

Out of the 353 patients, 239 (67.7%) developed AKI, of which 206 (86.9%) presented it on ICU admission. Among patients with AKI, 26% developed KDIGO stage 1, 25% stage 2 and 49% stage 3 AKI, and 95 (40%) underwent RRT, with a median time from ICU admission to the start of RRT of 1 (0–4) day, and a median duration of 5 (2–10) days (Table 2).

Patients with AKI more often had a history of CKD than those without AKI (16.7 versus 4.4%, p<0.01) (Table 1). In univariate analysis, AKI patients had higher severity scores, even after excluding the renal component (p<0.01), and more frequently required vasopressors (65.5% versus 39.5%, p<0.01) and invasive mechanical ventilation (41.4% versus 18.4%, p<0.01) (Table 2). ICU and hospital length of stay were similar in both patient groups, but ICU and hospital mortality were significantly higher in the AKI group (Table 2). While 3-year mortality was 77.2% in the overall population, a significant difference was observed between patients with AKI and those without (81.9% versus 66.7% respectively, p<0.01). This difference was observed at all time intervals (Figure 2). In multivariate analysis, however, the occurrence of AKI was not associated with long-term mortality. Only SAPS II, performance status ≥2 and refractory/relapsing HM were independent predictors of long term mortality (Table 4).

The requirement of RRT significantly worsens outcome, with higher severity, and higher mortality rates, with 3-year mortality reaching 91.6% (Table 2 and Figure 2). Among these patients, 57/95 (60%) died before ICU discharge and 35 (36.8%) were weaned from this procedure. Three patients remained dependent on RRT after ICU discharge meaning that almost all patients who survived their hospital stay were weaned of this procedure. The need for RRT tended to be associated with long term mortality without reaching statistical significance (Table 4).

Table 4. Predictors of long–term mortality

Predictors of long-term mortality	Univariate analysis (N=353)HR (95% CI)	p	Multivariate analysis (N=158)HR (95% CI)	p
SAPS II, per point	1.02 (1.02–1.03)	<0.001	1.02 (1.01–1.04)	<0.001
Non–renal SOFA, per point	1.10 (1.05–1.14)	<0.001		
Performance status ≥2	2.08 (1.44–2.99)	<0.001	1.79 (1.23–2.61)	0.003
Refractory/relapsing HM	1.70 (1.32–2.17)	<0.001	1.71 (1.18–2.47)	0.005
Acute kidney injury	1.82 (1.38–2.39)	<0.001		
RRT requirement	2.33 (1.79–3.02)	<0.001	1.50 (0.99–2.27)	0.058
Progression of HM at ICU discharge	3.54 (2.51–4.98)	<0.001		

CI: confidence interval; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; RRT: renal replacement therapy; HM: hematological malignancy; HR: hazard ratio; ICU: intensive care unit.

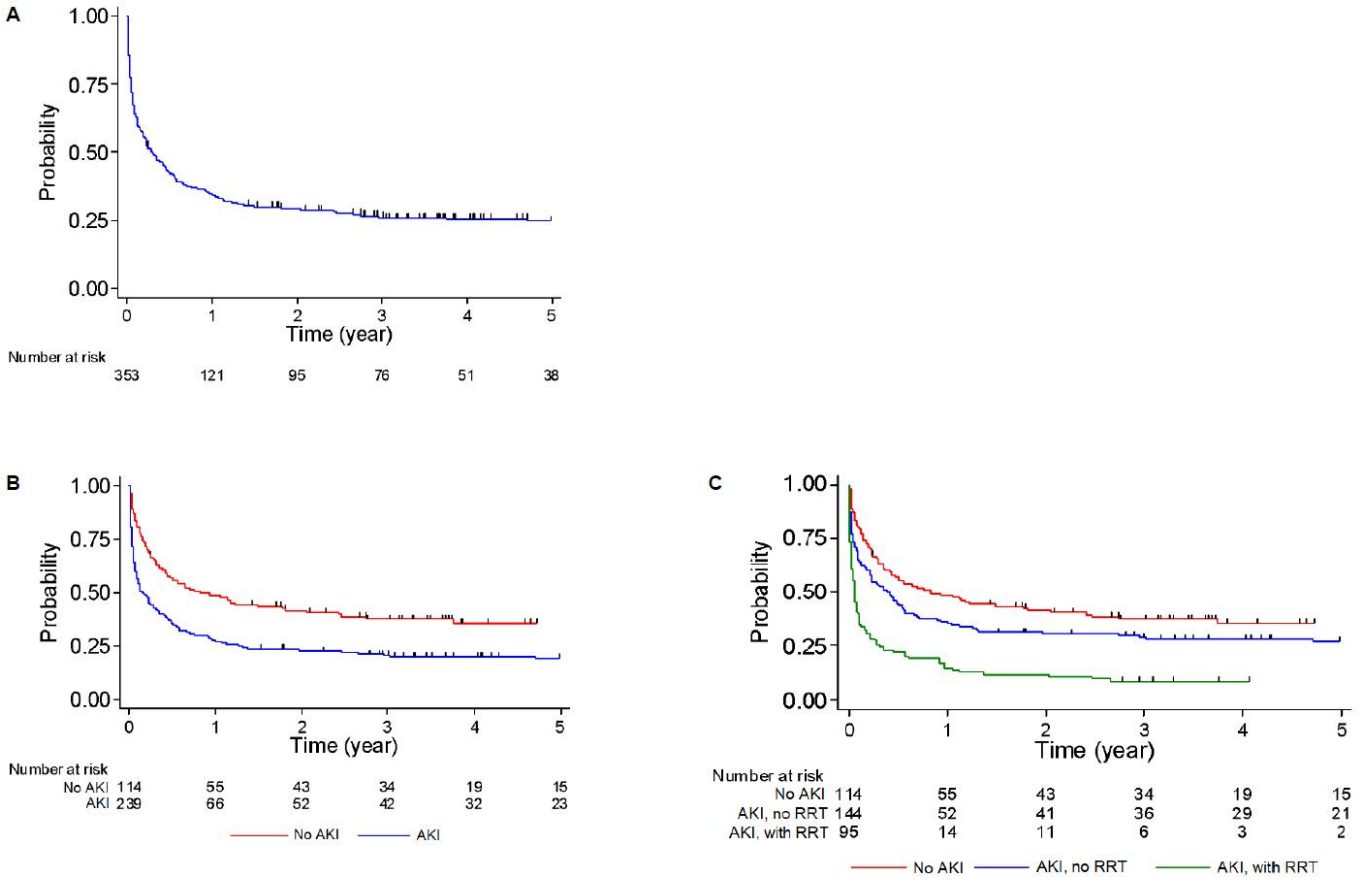


Figure 2: Kaplan Meier estimates of overall survival

(A) in all the population; (B) according to the occurrence of acute kidney injury (AKI); (C) according to the occurrence of AKI and its severity.

Assessment of renal function during follow-up showed that the percentage of patients who recovered or maintained their previous function was significantly higher in the group without AKI: 86.8% *versus* 69.9% ($p<0.01$). Indeed, median creatinine levels in surviving patients were significantly higher in the AKI than in the non-AKI group, irrespective of the time after discharge from the ICU ($p<0.01$) (Table 3).

After discharge from the hospital, initial hematological chemotherapy was maintained in 88/116 (75.8%) in the AKI group as compared to 76/104 (84.4%) in the no-AKI group, showing a significant difference ($p=0.03$) (Table 3). Supplementary Figure 1 presents overall relapse-free survival, showing that AKI is associated with a significantly worse prognosis. Noteworthy, RRT requirement seems to influence the rate of refractory or relapsing HM after discharge, with higher rates in RRT recipients. However, multivariate analysis showed that the occurrence of relapse of HM was only associated with SAPS II, PS, and its refractory status (Supplementary Table 1).

Discussion

The results of this single-center, 8-year retrospective study show that critically ill patients with hematological malignancies have a 42% in-hospital mortality and a poor long-term outcome, with a 3-year mortality rate of 77% and a relapse-free survival of 4 months. Acute kidney injury, with an incidence of 68%, worsened short and long- term mortality and reduced relapse-free survival, but multivariate analysis failed to reveal a significant association. Most surviving patients recovered or maintained their previous renal function, although this was less common in cases of AKI, particularly if it had required RRT. Despite the de-

velopment of AKI, treatment of the hematological disease in surviving patients was maintained or even modified, but not as a palliative measure.

The prognosis for critically ill patients with hematological malignancies remains unsatisfactory, particularly over the long term. In this cohort, 3-year mortality rate was at 77.2%, with nearly all deaths occurring the first year. An underlying malignancy in refractory or relapsed status significantly worsened the outcome. Higher SAPS II and impaired general condition (PS≥2) were also associated with a worse prognosis. Our findings corroborate what is currently widely accepted by most authors, and guide ICU management of these patients [7]. We first observed that more than 2/3 (67.7%) of our patients developed an AKI during their stay, and more than 1/3 of them (39.8%) required RRT. This prevalence is much higher than what is found in the general ICU population, but similar to what has already been described in patients presenting an AKI associated with HM admitted to the ICU [10–12, 19] . In addition, multiple myeloma was the leading cause of AKI, ahead of myeloid and lymphoid hemopathies, as previously reported [18, 19, 32]. The occurrence of AKI alters the prognosis of our patients both in the ICU and at discharge, as well as at every stage of long-term follow-up. This influence of AKI on the prognosis of our patients was correlated to its severity, with 3-year mortality rates of 91.6% in patients who required RRT.

Univariate analysis showed that patients with AKI had higher severity scores, more frequently required invasive mechanical ventilation and/or vasoconstrictor agents. However, multivariate analysis failed to show that the occurrence of AKI was associated with long-term mortality. The question arises as to whether the development of AKI is simply a reflection of the greater severity associated with the failure of more organs [33]. More than three-quarters of ICU survivors recovered or maintained their previous renal function. However, patients who developed AKI during their stay retained more impaired renal function in the long term than those who did not (69.9% versus 86.8%, p=0.01). Although recovery of renal function occurs in most patients, it depends on the cause of AKI. Recovery *ad integrum* is the rule in tumor lysis syndrome, whereas only 19% of patients requiring RRT in multiple myeloma will recover their previous renal function [14, 32]. In addition, subsequent renal stresses (chemotherapy lines, infections, etc.) may secondarily impair renal function in these patients. Noteworthy, the need for RRT was associated with higher mortality rates but among those who survived, 35/38 (92%) patients were weaned of this procedure, a rate higher than the reported 80% [32]. Previous studies have shown indeed that RRT does not independently lead to excess mortality [23, 34].

One of the most striking results of this study was that the initial hematology plan had to be modified in less than a quarter of survivors (42/206, 20.4%), although this proportion was significantly higher in those who suffered an AKI during their ICU stay (24.1% versus 15.5%, p=0.03). AKI was associated with mortality, but also with the inability of survivors to achieve complete remission [18]. Impaired renal function can sometimes lead to modification or even discontinuation of chemotherapy because of its potential deleterious effects. Modification of the therapeutic plan after an ICU stay has been reported in 20% of patients, including a change of molecule or dosage, or a plan becoming exclusively palliative [18, 25, 35]. This may be due to a lack of knowledge of drug pharmacokinetics in such circumstances, and also to the systemic deleterious effect of renal dysfunction compromising the efficacy of chemotherapy. In our patients, the therapeutic modification seemed to result in a change of curative rather than palliative regimen suggesting that the onset of AKI does not affect the subsequent treatment of hematological disease to any great extent. This observation is important to us, as it would encourage intensivists and hematologists not to consider the management of AKI of any severity as futile.

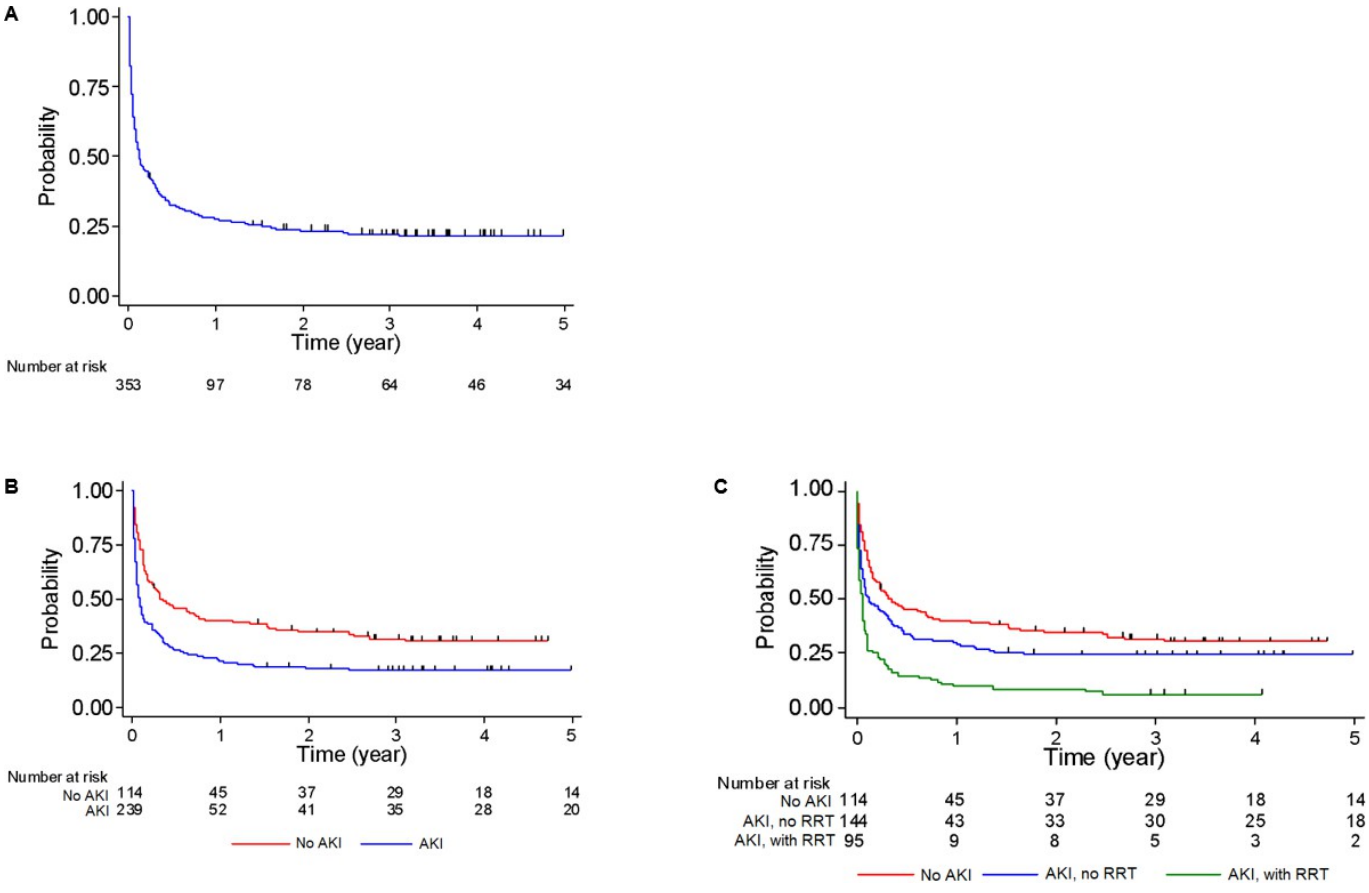
We must acknowledge some limitations to our study. First, it is a retrospective study, which therefore may be affected by various biases. Our study reflects real life, helping therefore physicians in their routine clinical practice. We took care, in addition, to homogenize our study population as much as possible to secure our results. Only patients with HM were included, excluding those with solid tumors as previously reported. Nevertheless, confounding factors inherent in retrospective analysis cannot be totally excluded. Second, it was limited to a single center. Our ICU admits most patients with hematologic malignancies who

present with severe, life-threatening conditions requiring prolonged MV and/or hemodynamic support, and has therefore gained substantial experience of these patients. As a result, our data cannot be generalized to all centers, particularly non-teaching hospitals. Third, data were extracted from patients' electronic records and some values may have been missing during collection. For example, the cause of AKI could not be specified, since it could have an impact on prognosis, as in the case of tumor lysis syndrome. Finally, the various HMs were classified as lymphoid, myeloid and myelomatous, without prejudging their aggressive or non-aggressive nature, which could have influenced patient outcome.

Conclusions

In conclusion, AKI frequently occurs in critically ill patients with hematological malignancies. It has a significant impact on long-term mortality, with a rate of 61.4% at 3 years, rising to 91.6% if RRT is required. Among patients who survive their ICU stay, two-thirds recover their previous renal function. More importantly, it does not substantially alter the subsequent therapeutic schema, which remains mostly curative. However, these data need to be confirmed by larger studies. Nevertheless, the results presented here could encourage intensivists not to limit the management of these patients because of the occurrence of AKI, even severe.

Supplementary Information



Supplementary Figure 1: Kaplan Meier estimates of relapse–free survival (A) in all the population; (B) according to the occurrence of acute kidney injury (AKI); (C) according to the occurrence of AKI and its severity.

Supplementary Table 1: Predictors of relapse

Predictors of relapse	Univariate analysis (N=353) HR (95% CI)	p	Multivariate analysis (N=158) HR (95% CI)	p
Age, per year	1.01 (1.00–1.02)	0.034		
SAPS II, per point	1.02 (1.01–1.03)	<0.001	1.02 (1.00–1.03)	0.016
Non–renal SOFA, per point	1.07 (1.03–1.11)	<0.001		
Performance status ≥2	2.38 (1.67–3.39)	<0.001	2.07 (1.44–2.99)	<0.001
Refractory/relapsing HM			1.93 (1.35–2.77)	<0.001
Acute kidney injury	1.72 (1.33–2.24)	<0.001		
RRT requirement	2.13 (1.65–2.75)	<0.001	1.44 (0.96–2.16)	0.08

CI: confidence interval; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; RRT: renal replacement therapy; HM: hematological malignancy; HR: hazard ratio.

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Availability of Data and Material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest Statement

The authors declare that they have no competing interests.

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