Nephrol Dial Transplant (2015) 30: 2006–2013
doi: 10.1093/ndt/gfv372

ndt
Nephrology Dialysis Transplantation

Original Article

Acute kidney injury in critically ill patients with haematological malignancies: results of a multicentre cohort study from the Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie

Michael Darmon[1], François Vincent[2], Emmanuel Canet[3], Djamel Mokart[4], Frédéric Pène[5], Achille Kouatchet[6], Julien Mayaux[7], Martine Nyunga[8], Fabrice Bruneel[9], Antoine Rabbat[5], Christine Lebert[10], Pierre Perez[11], Anne Renault[12], Anne-Pascale Meert[13], Dominique Benoit[14], Rebecca Hamidfar[15], Mercé Jourdain[16], Benoit Schlemmer[3], Sylvie Chevret[3], Virginie Lemiale[3] and Elie Azoulay[3]

[1]University Hospital, Saint-Etienne, France, [2]Avicenne University Hospital, Bobigny, France, [3]Saint-Louis University Hospital, Paris, France, [4]Paoli Calmette Institute, Marseille, France, [5]Cochin University Hospital, Paris France, [6]University Hospital, Angers, France, [7]Pitié-Salpétrière University Hospital, Paris, France, [8]Victor Provo Hospital, Roubaix, France, [9]Mignot Hospital, Versailles, France, [10]Montaigu Hospital, La Roche-sur-Yon, France, [11]Brabois University Hospital, Nancy, France, [12]Brest University Hospital, Brest, France, [13]Jules Bordet Institute, Brussels, Belgium, [14]Ghent University Hospital, Ghent, Belgium, [15]Albert Michallon University Hospital, Grenoble, France and [16]Salengro University Hospital, Lille, France

Correspondence and offprint requests to: Michael Darmon; E-mail: michael.darmon@chu-st-etienne.fr

ABSTRACT

Background. Cancer patients are at high risk for acute kidney injury (AKI), which is associated with high morbidity and mortality. We sought to appraise the incidence, risk factors, and outcome of AKI in a large multicentre cohort study of critically ill patients with haematological malignancies.

Methods. We used a retrospective analysis of a prospectively collected database. The study was carried out in 17 university or university-affiliated centres in France and Belgium between 2010 and 2012. AKI was defined according to the Acute Kidney Injury Network (AKIN) definition.

Results. Of the 1011 patients admitted into the intensive care unit (ICU) during the study period, 1009 were included in this study. According to the AKIN definition, 671 patients (66.5%) developed an AKI during their ICU stay, of which 258 patients (38.4%) were AKI stage 1, 75 patients (11.2%) AKI stage 2 and 338 patients (50.4%) AKI stage 3. After adjustment for confounders, main adverse risk factors of AKI were older age, severity [non-renal Sequential Organ Failure Assessment (SOFA)], history of hypertension, tumour lysis syndrome, exposure to nephrotoxic agents and myeloma. Hospital mortality was 44.3% in patients with AKI and 25.4% in patients without AKI ($P < 0.0001$). After adjustment for confounders, AKI was independently associated with hospital mortality [OR 1.65 (95% CI 1.19–2.29)]. Overall, 271 patients required renal replacement therapy (RRT), of whom 57.2% died during their hospital stay as compared with 31.2% ($P < 0.0001$) in those not requiring RRT.

Conclusion. Two-thirds of critically ill patients with haematological malignancies developed AKI. Hospital mortality in this population of patients developing AKI or requiring RRT is close to that in general ICU population.

Keywords: acute kidney injury, ICU, prognosis, renal replacement therapy, tumour lysis syndrome

INTRODUCTION

Acute kidney injury (AKI) in critically ill patients is common and is associated with substantial morbidity, mortality and consumption of healthcare resources. Moreover, it is also associated

with a substantial risk for long-term morbidity [1–5]. Cancer patients are at higher risk of AKI [6]. Sepsis, hypoperfusion, specific complications such tumour lysis syndrome or AKI resulting from the haematological malignancy itself or its treatment are the leading causes of AKI in patients with haematological malignancies [7–12].

Among general critically ill patients, AKI-related mortality exceeds 30% and reaches or exceeds 50% if renal replacement therapy (RRT) is required [2, 5, 13–15]. AKI in critically ill patients with haematological malignancies has been associated with a mortality rate >85% when RRT is required [10, 16]. In addition to the poor hospital mortality, AKI decreases the chances of achieving a complete remission and adversely affects long-term survival in these patients [9, 17, 18].

Most of the studies assessing prognosis in critically ill cancer patients with AKI have been retrospective monocentre cohort studies, raising doubts regarding the external validity of the presented results [7, 9, 10, 16]. In addition, the definition of AKI varied widely across these studies, precluding an accurate evaluation of both incidence and risk factors in these patients. Recent the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) definitions provided consensus definitions of AKI in order to allow comparison across studies [19, 20].

The primary objective of this study was to describe the incidence and risk factors of AKI according to the AKIN definition in a large multicentre cohort study of critically ill patients with haematological malignancies. Secondary objectives were to assess hospital mortality and report the influence of AKI, AKI severity and the need for RRT on outcomes among these patients.

MATERIALS AND METHODS

Study population

We performed a retrospective analysis of prospectively collected data from a recent study assessing prognosis in critically ill patients suffering from haematological malignancies [21]. Patients were prospectively included from 2010 to 2012. The study was carried out in 17 intensive care units (ICUs) in France and Belgium that belonged to a research network instituted in 2005. In all 17 centres, a senior intensivist and a senior haematologist are available around the clock and make ICU admission decisions together. In addition, the majority of the participating centres had at least one intensivist having a background in nephrology or nephrology as a primary specialty. The appropriate ethics committees approved this study and it was conducted in accordance with principles of the Declaration of Helsinki [21].

Definitions

Newly diagnosed haematological malignancies were defined as diagnosed within the past 4 weeks prior to or on ICU admission. Neutropenia was defined as a neutrophil count <500/mm^3. The Sequential Organ Failure Assessment (SOFA) score was computed at admission and then daily throughout the entire stay in the ICU; this score provides an estimate of the risk of death based on organ dysfunction [22]. A modified SOFA score at admission (SOFA score without its renal component) was also computed. The Eastern Cooperative Oncology Group performance status (PS) [23] and Charlson comorbidity index [24] were determined at ICU admission. Both leukaemia and lymphoma are already part of the Charlson comorbidity index [24].

The presence of AKI was evaluated in each patient at study inclusion. AKI was defined according to the AKIN classification scheme [20] as either serum creatinine elevation ≥26.4 μmoL/L (0.3 mg/dL) occurring within 48 h, serum creatinine elevation ≥150% from baseline or urine output <0.5 mL/kg/h for ≥6 h.

The lowest serum creatinine value in the 3 months preceding inclusion was taken as the baseline value. This baseline serum creatinine was to be reported as per protocol in every patient with a previous history of renal or urological disorder (143 of the studied patients). When there was no history of renal disorder, the baseline creatinine was assumed to be normal and was back-calculated using the Modification of Diet in Renal Disease (MDRD) formula (four-variable equation) while assuming an eGFR of 75 mL/min/1.73 m^2 before ICU admission as suggested by the Acute Dialysis Quality Initiative (ADQI) [19, 25].

Chronic kidney disease (CKD) was defined as the association of a pre-existing CKD and according to the KDIGO definition [26].

Reasons for ICU admission were recorded based on the main symptoms at ICU admission. Acute respiratory failure was defined as oxygen saturation <90% or a partial pressure of oxygen in arterial blood (PaO_2) <60 mmHg on room air combined with severe dyspnoea at rest with an inability to speak in sentences or a respiratory rate >30 breaths per minute or clinical signs of respiratory distress [27]. Shock was defined as previously reported [28]. Life-supporting interventions, RRT, anti-infectious agents, prophylactic treatments, urate oxidase use and diagnostic procedures were administered at the discretion of the attending intensivists, who followed best clinical practices and guidelines. Chemotherapy, corticosteroids, haematopoietic growth factors, immunosuppressive drugs and other cancer-related treatments were prescribed by the haematologist in charge of each patient in accordance with institutional guidelines. Tumour lysis syndrome was defined according to the 2008 consensus definition [29].

Aetiologic diagnoses and definition of sepsis were made by consensus by the intensivists, haematologists and consultants, according to recent definitions [21, 30]. In particular, aetiologies of pulmonary involvement were diagnosed based on predefined criteria [27]; for possible or probable invasive pulmonary aspergillosis, the most recent definitions were used [31].

Statistical analysis

Results are reported as medians and quartiles [interquartile range (IQR)] or number and percent. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate, and continuous variables using the non-parametric Wilcoxon test or the Mann–Whitney test.

We performed logistic regression analyses to identify variables statistically significantly associated with AKI, RRT and hospital mortality, as measured by the estimated OR with the 95% CI. Variables yielding P-values <0.20 in the univariate analyses or considered clinically relevant were entered into a backward stepwise logistic regression model. Non-log-linear

continuous variables were dichotomized. The covariates were entered into the model with critical entry and removal P-values of 0.20 and 0.1, respectively. Multicollinearity and interactions were tested. The Hosmer–Lemeshow test was used to check goodness-of-fit of the logistic regression.

Survival curves have been constructed according to the Kaplan–Meier method. Comparison across severity class of AKI was performed using the log-rank test.

All tests were two-sided and P-values <0.05 were considered statistically significant. Statistical tests were done using the SPSS 13 software package (IBM, Armonk, NY, USA).

RESULTS

Patients' characteristics

Among the 1011 patients, data regarding renal function were evaluable for 1009 patients who were included in this study (Figure 1). Table 1 reports the characteristics of the patients. Overall, 612 patients (60.7%) were male and the median age was 60 years (range 49–70). The median SOFA score at ICU admission was 6 (range 3–9). The Charlson comorbidity index was 4 (range 2–5) and 195 (19.3%) patients had a poor performance status (bedridden/disabled). Of the included patients, 349 (34.6%) had acute leukaemia, 396 (39.2%) a non-Hodgkin's lymphoma and 126 (12.5%) had myeloma. Two hundred and thirty-three patients (23.1%) were in partial or complete remission and 144 had undergone allogeneic stem cell transplantation (14.3%). Last, 648 had ongoing cancer chemotherapy with a median delay between last cure and ICU admission of 19 days (range 8–70).

The delay between hospital and ICU admission was 4 days (range 1–6). Most patients were admitted from a hospital ward [742 (73.5%)], including 183 patients admitted within 24 h of hospital admission. Two hundred and sixty-seven patients were admitted directly to the ICU.

The main reasons for ICU admission (one or more) were acute respiratory failure in 630 patients (62.4%), shock in 428 (42.4%), acute kidney injury in 308 (30.5%), coma in 225 (22.3%) and urgent chemotherapy in 70 (6.9%). At admission, 652 patients presented with sepsis (64.6%), including 285 patients with sepsis/septic shock (28.2%).

AKI and risk factors

According to the AKIN definition, 671 patients [66.5% (95% CI 63.6–69.4)] had AKI during their ICU stay, including 258 patients (38.4%) with AKI stage I, 75 patients (11.2%) with AKI stage II and 338 patients (50.4%) with AKI stage 3 (Figure 1). Across the participating centres, the AKI proportion ranged from 40% (95% CI 18.5–61.5) to 84.4% (95% CI 73.8–95). Most of the patients [$n = 555$ (82.7%)] had AKI at ICU admission: 56 patients (8.3%) at Day 1, 40 patients (6.0%) at Day 2 and 20 patients (3.0%) at Day 3 or later during their ICU stay. Among patients with AKI, AKI was defined by oliguria in 181 patients (27.0%), creatinine elevation in 287 patients (42.7%) and by both in 203 patients (30.3%).

Sepsis and septic shock were the main risk factors identified with AKI (Table 1 and Supplementary Figure S1). One hundred

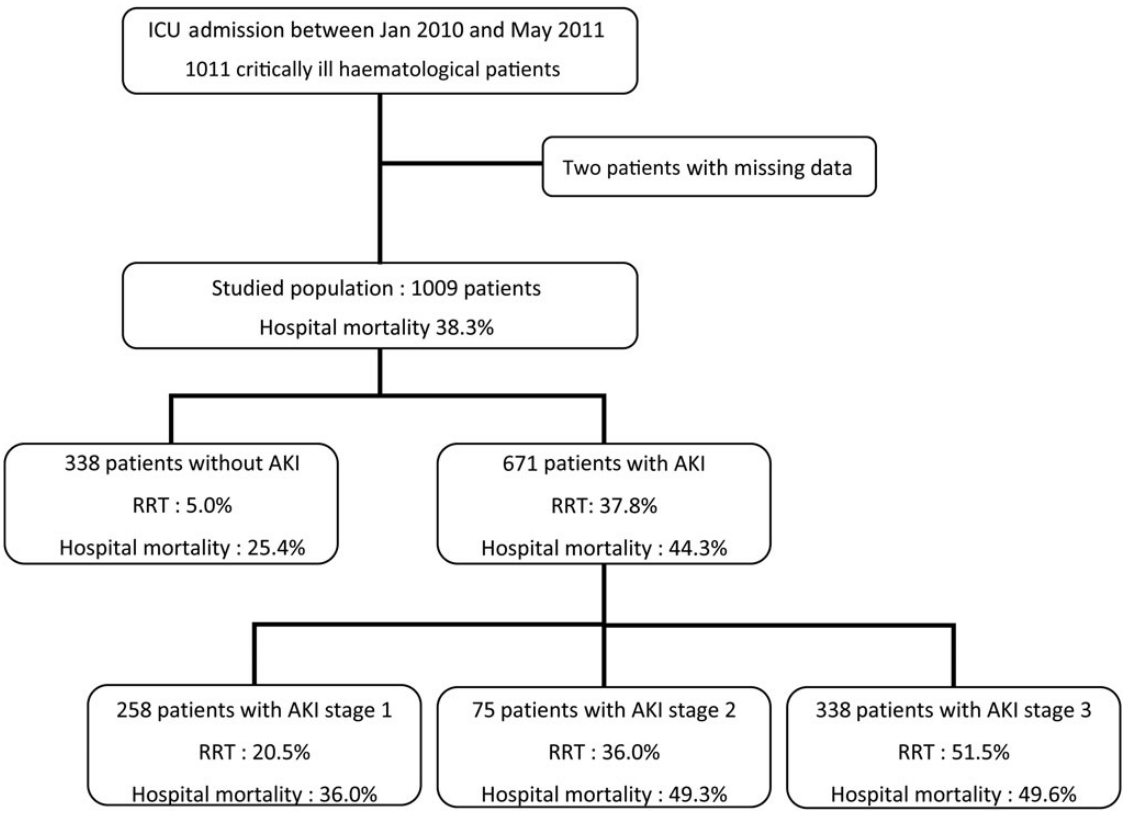

FIGURE 1: Flow chart of patients admitted during the study period.

Table 1. Patient characteristics

	AKI (*N* = 671)	No AKI (*N* = 338)	P-value
Male gender, *n* (%)	427 (63.3)	185 (54.7)	0.08
Age (years), median (range)	62 (52–71)	57 (44–66)	<0.0001
Poor performance status, *n* (%)	65 (19.3)	132 (19.2)	0.99
SOFA score at ICU admission [22], median (range)	6 (4–10)	4 (2–7)	<0.0001
Charlson comorbidity index [24], median (range)	4 (3–6)	4 (2–5)	<0.0001
Baseline creatinine (μmol/L), median (range)	88 (80–97)	86 (80–97)	0.51
Body mass index (kg/m²), median (range)	24.2 (20.9–27.6)	23.9 (20.7–26.7)	0.34
Characteristics at admission, median (range)			
Serum creatinine	136 (91–224)	70 (54–89)	<0.0001
Diuresis (L/day)	0.8 (0.4–1.5)	1.7 (1.2–2.6)	<0.0001
Leucocytes (G/L)	6.3 (0.8–16.9)	4.0 (0.8–12.3)	0.06
Hemoglobin (g/dL)	8.9 (7.7–10.2)	9.2 (7.9–10.3)	0.31
Platelets (G/L)	65 (29–138)	58 (29–145)	0.94
Lactate dehydrogenase (× normal values)	1 (1–3)	1 (1–2)	0.84
Lactates	2.2 (1.3–4.9)	1.7 (1.1–3.2)	<0.0001
Underlying malignancy, *n* (%)			
Acute myeloid leukaemia	163 (24.3)	110 (32.5)	0.005
Acute lymphoblastic leukaemia	44 (6.6)	32 (9.5)	0.10
Non-Hodgkin lymphoma	268 (39.9)	128 (37.9)	0.41
Myeloma	101 (15.1)	25 (7.3)	0.0005
Miscellaneous malignancies	95 (14.1)	43 (12.7)	0.56
Partial/complete remission	153 (22.8)	80 (25.2)	0.76
Stem cells transplantation, *n* (%)			
Autologous	65 (9.7)	39 (11.5)	0.36
Allogeneic	99 (14.8)	45 (13.3)	0.53
Factors associated with AKI, *n* (%)			
Nephrotoxic agent	170 (25.3)	31 (9.2)	<0.0001
Including calcineurin inhibitors	67 (10.0)	20 (5.9)	0.03
Tumour lysis syndrome	83 (12.4)	11 (3.3)	<0.0001
CKD according to KDIGO	103 (15.3)	24 (7.1)	<0.0001
Including Stage G1	11 (1.6)	1 (0.3)	
Stage G2	29 (4.3)	10 (3.0)	
Stage G3	41 (6.1)	7 (2.1)	
Stage G4	15 (2.2)	4 (1.2)	
Stage G5	7 (1.0)	2 (0.6)	
Chronic heart failure	95 (14.2)	34 (10.6)	0.07
Coronary artery disease	63 (9.4)	12 (3.6)	0.008
Diabetes mellitus	78 (11.6)	31 (9.2)	0.37
History of hypertension	212 (31.6)	60 (17.8)	<0.0001
Sepsis	435 (64.8)	217 (64.2)	0.84
Including severe sepsis/septic shock	210 (31.3)	75 (22.2)	0.006
Organ support at ICU admission, *n* (%)			
Mechanical ventilation	211 (31.7)	73 (21.7)	0.0009
Non-invasive mechanical ventilation	101 (15.2)	64 (19.2)	0.11
Vasopressors	241 (34.9)	80 (23.7)	<0.0001
RRT	107 (15.9)	5 (1.5)	<0.0001
Transfusion of red blood cells	306 (45.6)	115 (34.0)	0.0004
Number of PRBCs from day 1 to day 7, median (range)	0 (0–2)	0 (0–2)	0.002
RRT during ICU stay, *n* (%)	254 (37.8)	17 (5.0)	<0.0001
ICU mortality, *n* (%)	226 (33.7)	52 (15.4)	<0.0001
Hospital mortality, *n* (%)	297 (44.3)	86 (25.4)	<0.0001

PRBCs, packed red blood cells.

and twenty-seven patients (12.6%) had a history of CKD, 272 (27.0%) a history of hypertension and 109 (10.8%) had diabetes mellitus. Concomitant nephrotoxic agents were identified in 201 patients (19.9%), including calcineurin inhibitors in 87 patients (8.6%), aminoglycosides in 29 patients (2.9%), glycopeptides in 25 (2.5%), angiotensin-converting enzymes inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in 17 patients (1.7%) and iodinated contrast media in 10 patients (0.9%). Ninety-four patients had acute tumour lysis syndrome (9.3%). The rate of AKI was similar in patients who received cancer chemotherapy the week preceding ICU admission (66.6 versus 63.8%; P = 0.69).

After adjustment for confounders, older age, initial severity as assessed by a modified SOFA score (SOFA score without its renal component), history of hypertension, tumour lysis syndrome, exposure to a nephrotoxic agent and myeloma as an underlying malignancy were independently associated with AKI (Table 2). When forced in the final model, neither

Table 2. Independent predictors of AKI (conditional backward logistic regression)

	OR	95% CI	P-value
Age (per year)	1.02	1.01–1.030	0.001
History of hypertension	1.53	1.06–2.21	0.02
Tumour lysis syndrome	4.66	2.38–9.15	<0.0001
Nephrotoxic agents	3.55	1.92–6.57	<0.0001
Myeloma	1.93	1.18–3.15	0.01
SOFA score at admission (per point)[a]	1.16	1.11–1.21	<0.0001

Hosmer–Lemeshow goodness-of-fit: $\chi^2 = 9.05$; P = 0.34.
[a]Modified SOFA score at admission (SOFA score without its renal component) [22].

Table 3. Independent predictors of hospital mortality (conditional backward logistic regression)

	OR	95% CI	P-value
Allogeneic SCT	3.10	1.97–4.89	<0.0001
SOFA (per point)[a]	1.18	1.13–1.23	<0.0001
Any stage of AKI	1.65	1.19–2.29	0.003
Cardiac arrest as reason for admission	12.50	1.43–109.3	0.02
Acute respiratory failure at admission	1.53	1.13–2.06	0.006
Aspergillosis	2.01	1.13–3.57	0.02
Charlson index [24] (per point)	1.09	1.02–1.16	0.008
Myeloma	0.58	0.37–0.91	0.02
Partial or complete remission	0.50	0.34–0.74	0.001

Hosmer–Lemeshow goodness-of-fit: $\chi^2 = 5.57$; P = 0.62; C-stat = 0.71.
SCT, stem cells transplantation.
[a]Modified SOFA score at admission (SOFA score without its renal component) [22].

transfusion of red blood cells nor the number of packed red blood cells was selected, nor did they modify the final model.

Influence of AKI on outcome

Overall, 297 patients with AKI (44.3%) and 86 patients (25.4%) without AKI died during their hospital stay (P < 0.0001; Supplementary Figure S2). The decision to forgo life-sustaining therapy was made in 228 patients (22.6%), including 183 patients with AKI (27.3%) and 44 patients without AKI (13.0%; P < 0.0001). Among these patients, 165 died during their ICU stay (72.4%) and 195 during their hospital stay (85.6%).

After adjustment for confounders, AKI remained associated independently with hospital mortality [OR 1.65 (95% CI 1.19–2.29); Table 3]. Six additional factors were independently associated with poor outcome, namely allogeneic stem cells transplantation, severity as assessed by the modified SOFA score (SOFA score without its renal component), cardiac arrest and acute respiratory failure as the main reasons for ICU admission, aspergillosis and Charlson comorbidity index. Two factors were associated with hospital survival, namely myeloma as an underlying malignancy and complete or partial remission of the underlying malignancy at ICU admission (Table 3).

A sensitivity analysis was performed after exclusion of patients with AKI after Day 0 (ICU admission) and the final model and influence of AKI on outcome remain unchanged.

Hospital mortality in patients with AKI stages 1, 2 and 3 were 36.0, 49.3 and 49.6%, respectively (P < 0.0001; Figures 1 and 2). The adjusted influence of AKI stage on outcome is reported in Supplementary Table S1. Similarly, patients with AKI defined by oliguria alone had a lower mortality (34.3%) than patients

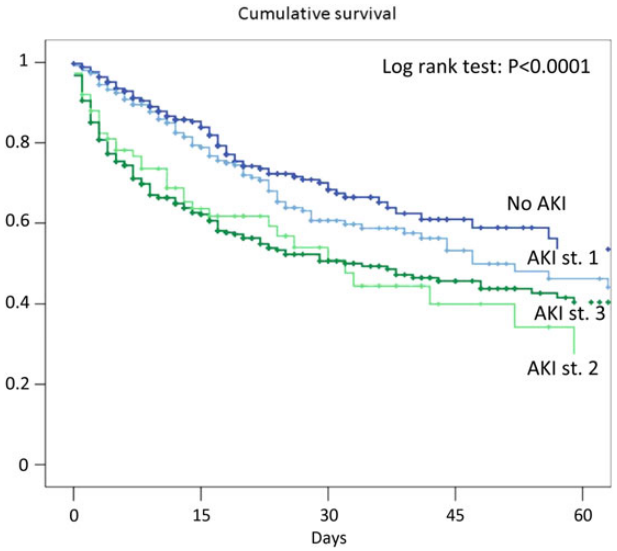

FIGURE 2: Cumulative survival according to AKI and its severity (no AKI: dark blue line; AKI stage 1: light blue line; AKI stage 2: light green line; AKI stage 3: deep green line). Comparison according to log-rank test; P < 0.0001.

with serum creatinine elevation (41.6%) or patients who met both AKI criteria (57.1%; P < 0.001).

RRT

Overall, 271 patients (26.9%) received RRT during their ICU stay, including 17 patients (6.2% of patients receiving RRT) without AKI, 53 patients (19.6%) with AKI stage 1, 27 patients with AKI stage 2 (9.9%) and 174 patients with AKI stage 3 (64.2%). The delay between maximal AKI stage and RRT initiation was 1 day (range 0–1). The initial modality of RRT was continuous RRT [continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), continuous venovenous haemodiafiltration (CVVHDF)] in 136 patients and intermittent haemodialysis (IHD) or sustained low-efficiency dialysis (SLED) in 135 patients. Among ICU survivors, 15 patients (12.9%) remain dependent on RRT, including 11 patients initially treated by IHD (16.4%) and 4 patients initially treated by continuous RRT (8.1%; P = 0.26).

After adjustment for confounders, patients with vasopressors were more likely to be treated initially with continuous RRT [OR 1.94 (95% CI 1.16–3.25)] and patients with CKD to receive IHD (Supplementary Table S2).

Overall, 155 patients requiring RRT (57.2%) and 230 patients who did not require RRT (31.2%) died during their hospital stay (P < 0.0001; Figure 3). After adjustment for confounders, RRT modality was not associated with outcome (Supplementary Table S3). Similarly, when maximal AKI stage or delay between maximal AKI stage and RRT were forced in the final model, they did not modify the final model and were not selected.

DISCUSSION

This study describes the incidence of AKI according to AKIN classification, risk factors of AKI and outcomes in 1009

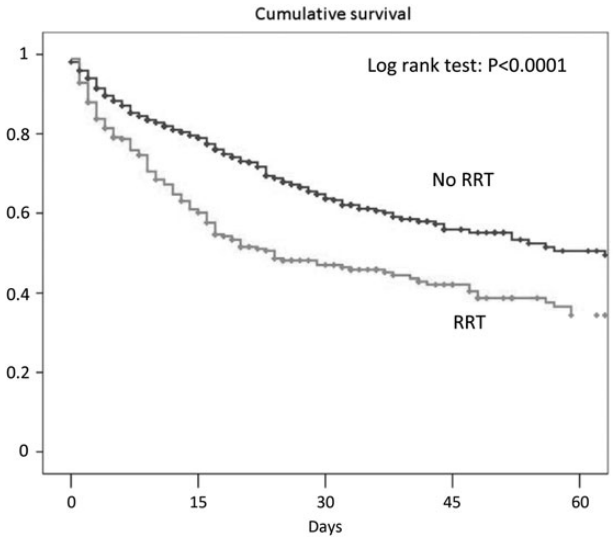

FIGURE 3: Cumulative survival according to RRT requirement (no RRT: dark line; RRT: grey line). Comparison according to log-rank test; $P < 0.0001$.

critically ill patients with haematological malignancies admitted to 17 ICUs between 2010 and 2012. This large multicentre study provides three valuable pieces of information. First, our results confirm the high incidence of AKI in this population. Hence, two-thirds of the patients develop any stage of AKI during ICU stay compared with 30–40% in the general ICU population [5, 13]. Second, although both AKI and RRT were associated with a higher mortality in the studied population, the mortality rates of both patients with AKI and patients requiring RRT approach that of the general ICU population with similar illness severity [2, 5, 13, 14, 19]. Last, our study provides several identified risk factors of AKI in this specific population. Interestingly, besides the usual risk factors of AKI (age, previous history of hypertension or pre-existing CKD), only two factors related to the underlying malignancy were independently associated with AKI, namely tumour lysis syndrome and myeloma.

In keeping with previous findings, our study underlines the high prevalence of AKI in critically ill patients with haematological malignancies [6, 9, 18]. In our study, two-thirds of these patients admitted in the 17 participating centres experienced any degree of AKI and one-third experienced a stage 3 AKI. These results contrast with the incidence in the general population of hospitalized patients (15–20% of AKI) or in critically ill patients (30–40%) according to AKIN or KDIGO-equivalent definitions [5, 13, 32–34]. Our results are nevertheless in accordance with previous studies in this field. Hence, previous studies of our group performed in patients with newly diagnosed high-grade haematological malignancies suggested that up to 20% of the cancer patients and up to 36% of patients with high-grade malignancies experienced AKI [18, 35]. Additionally, up to 69% of these patients develop AKI when ICU admission is required [8, 9, 36]. A previous study performed by Soares *et al.* [10] reported an AKI prevalence of 32% using RIFLE (Risk of renal injury/Injury to the kidney/Failure of kidney function/Loss of kidney function/End stage disease) criteria. However, 80% of the studied patients had solid tumours, a condition that may be less associated with specific causes for AKI. Hence, in this study, only 10% of the factors associated with AKI were related to the underlying malignancies. In a population-based study performed in the health region of Calgary (Canada), Bagshaw *et al.* [6] underlined the higher risk of AKI in cancer patients (relative risk of developing AKI was as high as 9.9). Our study confirms the high incidence of AKI according to the AKIN definition in the studied population.

Additionally, this multicentre study provides information regarding the outcome of critically ill haematological patients with AKI. Hence, in our study, hospital mortality was 44.2% in patients with AKI and 57.2% in patients requiring RRT. Although comparison with previous studies is difficult given the differences in case mix and patient severity, the hospital mortality of AKI patients in our study is similar to the 25–40% range reported in previous large cohort studies using objective and recognized AKI criteria [2, 5, 13, 32]. Similarly, two large multicentre studies assessing dialysis doses in critically ill patients reported hospital mortality rates of 44% [15] and 50% [14]. Our results contrast with the high in-hospital mortality reported by previous studies [10, 16, 37] and suggest that the improved outcome in critically ill cancer patients also includes this specific population of patients [38–40]. Our results indicate that the presence of AKI in itself should not justify denial for ICU admission in patients with haematological malignancies. Of note, although hospital mortality in multiple myeloma patients was similar to the hospital mortality in the study population (31.0 versus 39.7%; $P = 0.08$), multiple myeloma was found to be protective for hospital mortality when AKI was taken into account. In keeping with previous studies, this suggests AKI is a major prognostic factor in myeloma patients admitted in the ICU [41].

Our study has several limitations that need to be taken into account. First, despite the multicentre design, we cannot exclude selection bias due to local admission policies. However, each participating ICU worked in close collaboration with the haematologists, and both senior intensivists and haematologists were available at any time. Therefore our results may not be extrapolated to ICUs or hospitals with lower physician availability or with lower staffing. Additionally, most of the patients with AKI already had an AKI at ICU admission, suggesting renal injury occurred during the hospital stay or before ICU admission. The delay between AKI occurrence and ICU admission was not recorded in this study and may have influenced patients' outcomes. Previous studies suggested a shorter delay between organ dysfunction and ICU admission to be beneficial in the general population of critically ill cancer patients or those with specific conditions such as severe sepsis [21, 42]. Specific studies are needed to assess the influence of timing before ICU admission in patients with AKI. Additionally, the choice to continue ACEIs or ARBs along with nephrotoxic agents is debatable. A recent study suggested that these agents were not associated with structural damage biomarkers in surgical patients [43]. Nevertheless, ACEIs and ARBs were associated with both increased incidence and increased severity of AKI [43]. Last, baseline serum creatinine was missing for patients without

urologic or renal pre-existing disease. Therefore, and in accordance with current guidelines, baseline creatinine was back-calculated from the MDRD assuming a 75 mL/kg/m² glomerular filtration rate [19, 25]. Although validated in previous works [44], this imputation may overestimate incidence of AKI by nearly 10% and misclassify the severity of AKI in up to 30% of patients [45]. This misclassification usually occurs as result of the assumption of a low normal baseline renal function (thus ignoring pre-existing CKD) but also assuming that patients have comparable muscle mass as the age-, gender- and weight-matched patients. However, baseline creatinine was recorded for every patient with a history of urologic or renal pre-existing diseases, limiting the risk of unrecognized CKD in this cohort. Additionally, body mass index was within the normal range for a European ICU population [46] and similar in patients with and without AKI despite the underlying malignancy. This is likely to have mitigated biases related to the use of MDRD-estimated baseline creatinine in this database.

In summary, in this large multicentre cohort study including critically ill patients with haematological malignancies we found a 67% incidence of AKI. Half of the patients experienced severe AKI according to the AKIN classification and 27% of the overall population required RRT. In addition to the usual risk factors of AKI, myeloma and tumour lysis syndrome were the main additional factors associated with AKI in this population of patients. Hospital mortality approached that reported in the general ICU population with AKI. Additional studies are needed to further explore long-term consequences of AKI on remission rate and to evaluate specific preventive measures in this population of patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

This article reports results of an ancillary study of the TRIALOH study (Azoulay *et al.* J Clin Oncol 2013). This point is acknowledged in the article and the initial study is cited (reference 21). This study was supported by a grant of the French Ministry of Health (PHRC AOM 08235).

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES

1. Chertow GM, Burdick E, Honour M *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16: 3365–3370
2. Cruz DN, Bolgan I, Perazella MA *et al.* North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEiPHROS-AKI): targeting the problem with the RIFLE criteria. Clin J Am Soc Nephrol 2007; 2: 418–425
3. Coca SG, Yusuf B, Shlipak MG *et al.* Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009; 53: 961–973
4. Stads S, Fortrie G, van Bommel J *et al.* Impaired kidney function at hospital discharge and long-term renal and overall survival in patients who received CRRT. Clin J Am Soc Nephrol 2013; 8: 1284–1291
5. Nisula S, Kaukonen K-M, Vaara ST *et al.* Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013; 39: 420–428
6. Bagshaw SM, Laupland KB, Doig CJ *et al.* Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care 2005; 9: R700–R709
7. Darmon M, Thiery G, Ciroldi M *et al.* Should dialysis be offered to cancer patients with acute kidney injury? Intensive Care Med 2007; 33: 765–772
8. Darmon M, Vincent F, Camous L *et al.* Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Réanimation Respiratoire et Onco-Hématologique. Br J Haematol 2013; 162: 489–497
9. Canet E, Zafrani L, Lambert J *et al.* Acute kidney injury in patients with newly diagnosed high-grade hematological malignancies: impact on remission and survival. PLoS One 2013; 8: e55870
10. Soares M, Salluh JIF, Carvalho MS *et al.* Prognosis of critically ill patients with cancer and acute renal dysfunction. J Clin Oncol 2006; 24: 4003–4010
11. Lameire N, Van Biesen W, Vanholder R. Acute renal problems in the critically ill cancer patient. Curr Opin Crit Care 2008; 14: 635–646
12. Benoit DD, Hoste EA. Acute kidney injury in critically ill patients with cancer. Crit Care Clin 2010; 26: 151–179
13. Joannidis M, Metnitz B, Bauer P *et al.* Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 2009; 35: 1692–1702
14. Palevsky PM, Zhang JH, O'Connor TZ *et al.* Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008; 359: 7–20
15. Bellomo R, Cass A, Cole L *et al.* Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009; 361: 1627–1638
16. Benoit DD, Hoste EA, Depuydt PO *et al.* Outcome in critically ill medical patients treated with renal replacement therapy for acute renal failure: comparison between patients with and those without haematological malignancies. Nephrol Dial Transplant 2005; 20: 552–558
17. Munker R, Hill U, Jehn U *et al.* Renal complications in acute leukemias. Haematologica 1998; 83: 416–421
18. Lahoti A, Kantarjian H, Salahudeen AK *et al.* Predictors and outcome of acute kidney injury in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome. Cancer 2010; 116: 4063–4068
19. Kellum JA, Lameire N, for the KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013; 17: 204
20. Mehta RL, Kellum JA, Shah SV *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31
21. Azoulay E, Mokart D, Pène F *et al.* Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol 2013; 31: 2810–2818
22. Vincent JL, Moreno R, Takala J *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22: 707–710
23. Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649–655
24. Charlson ME, Pompei P, Ales KL *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–383
25. Ad-hoc working group of ERBP, Fliser D, Laville M *et al.* A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving

Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. Nephrol Dial Transplant 2012; 27: 4263–4272
26. Chapter 1: definition and classification of CKD. Kidney Int Suppl 2013; 3: 19–62
27. Azoulay E, Mokart D, Lambert J *et al.* Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 2010; 182: 1038–1046
28. Mourad M, Chow-Chine L, Faucher M *et al.* Early diastolic dysfunction is associated with intensive care unit mortality in cancer patients presenting with septic shock. Br J Anaesth 2014; 112: 102–109
29. Coiffier B, Altman A, Pui C-H *et al.* Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008; 26: 2767–2778
30. Levy MM, Fink MP, Marshall JC *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29: 530–538
31. De Pauw B, Walsh TJ, Donnelly JP *et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008; 46: 1813–1821
32. Bagshaw SM, George C, Bellomo R, for the ANZICS Database Management Committe. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant 2008; 23: 1569–1574
33. Zeng X, McMahon GM, Brunelli SM *et al.* Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. Clin J Am Soc Nephrol 2014; 9: 12–20
34. Susantitaphong P, Cruz DN, Cerda J *et al.* World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol 2013; 8: 1482–1493
35. Salahudeen AK, Doshi SM, Pawar T *et al.* Incidence rate, clinical correlates, and outcomes of AKI in patients admitted to a comprehensive cancer center. Clin J Am Soc Nephrol 2013; 8: 347–354
36. Samuels J, Ng CS, Nates J *et al.* Small increases in serum creatinine are associated with prolonged ICU stay and increased hospital mortality in critically ill patients with cancer. Support Care Cancer 2011; 19: 1527–1532
37. Brunet F, Lanore JJ, Dhainaut JF *et al.* Is intensive care justified for patients with haematological malignancies? Intensive Care Med 1990; 16: 291–297
38. Darmon M, Azoulay E. Critical care management of cancer patients: cause for optimism and need for objectivity. Curr Opin Oncol 2009; 21: 318–326
39. Zuber B, Tran T-C, Aegerter P *et al.* Impact of case volume on survival of septic shock in patients with malignancies. Crit Care Med 2012; 40: 55–62
40. Legrand M, Max A, Peigne V *et al.* Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 2012; 40: 43–49
41. Haynes RJ, Read S, Collins GP *et al.* Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. Nephrol Dial Transplant 2010; 25: 419–426
42. de Montmollin E, Tandjaoui-Lambiotte Y, Legrand M *et al.* Outcomes in critically ill cancer patients with septic shock of pulmonary origin. Shock 2013; 39: 250–254
43. Coca SG, Garg AX, Swaminathan M *et al.* Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant 2013; 28: 2787–2799
44. Závada J, Hoste E, Cartin-Ceba R *et al.* A comparison of three methods to estimate baseline creatinine for RIFLE classification. Nephrol Dial Transplant 2010; 25: 3911–3918
45. Siew ED, Matheny ME, Ikizler TA *et al.* Commonly used surrogates for baseline renal function can impact acute kidney injury classification and prognosis. Kidney Int 2010; 77: 536–542
46. Borel A-L, Schwebel C, Planquette B *et al.* Initiation of nutritional support is delayed in critically ill obese patients: a multicenter cohort study. Am J Clin Nutr 2014; 100: 859–866

Received for publication: 19.5.2015; Accepted in revised form: 22.9.2015