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Original Article

ORIGINAL ARTICLE

Haematological malignancies and acute kidney injury requiring nephrology consultation: challenging the worst of the worst

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Abstract

Background: Acute kidney injury (AKI) often complicates the course of haematological malignancies (HMs) and confers a worse prognosis. The majority of these patients are managed by the attending physician, yet, a small group, mostly coincident with the worst presentation and outcomes, requires nephrology consultation, challenging the clinician with ethical issues regarding the decision to initiate or forgo renal support therapy. The purpose of this work is to identify the prognostic determinants for in-hospital mortality in this population.

Methods: A retrospective, observational chart review was undertaken at a single tertiary referral oncological centre. We reviewed the medical records of in-hospital patients with AKI and HM between 1 January 1995 and 31 December 2014 who met the criteria for RIFLE (Risk, Injury, and Failure; and Loss; and End-stage kidney disease) classification of I or higher and were followed by a nephrologist.

Results: Three hundred and forty-five patients were included in the study. Predictors of in-hospital death in patients with HM and AKI were septic shock [odds ratio (OR) 4.290 (95% CI 2.058–8.943)], invasive mechanical ventilation (IMV) [OR 4.305 (95% CI 2.075–8.928)] and allogeneic stem cell transplantation (SCT) [OR 2.232 (95% CI 1.260–3.953)]. The combination of each risk factor was used to estimate the probability of dying. Patients with all three risk factors had a risk of death of 86%.

Conclusions: Septic shock, IMV and allogeneic SCT were identified as independent predictors of death in patients with HM and AKI, with only a small chance of survival if all three were present. Depending on the combination of risk factors, the indication for aggressive life support therapies, such as RST, might be questionable.

Key words: AKI, dialysis, haemodialysis, prognosis, survival analysis

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Introduction

In recent years, many advances have been made concerning treatment and supportive care of haematological diseases (HMs). However, acute kidney injury (AKI) remains a common complication of these diseases and/or their treatment and is associated with high morbidity and mortality. Several contributors might be related to the high rates of AKI, including myeloma cast nephropathy; leukaemic infiltration; tumour lysis syndrome (TLS); glomerulonephritis; nephrotoxicity induced by chemotherapy, antibiotics, contrast media or non-steroidal anti-inflammatory drugs; volume depletion due to vomiting, diarrhoea, anaemia and sepsis or obstructive nephropathy.

In addition to being a population particularly susceptible to renal disease, patients with cancer who develop AKI have worse outcomes [1]. Kidney failure may compromise the success of anticancer treatments by altering target drug doses, resulting either in overdosing and increased toxicity or in suboptimal doses, hence reducing chances of remission [2, 3]. Renal disease also limits access to potentially curative therapies and excludes patients from clinical trials.

Patients with HM seem to be among cancer patients especially at high risk of AKI. In a Danish population-based study of incident cancer patients, multiple myeloma patients had, along with kidney and liver cancer, the highest 1-year risk of AKI [4]. Other subgroups particularly at high risk are those with acute lymphoma or leukaemia undergoing induction chemotherapy. Lahoti *et al.* [5] published a series of 537 patients with either acute myelogenous leukaemia or high-risk myelodysplastic syndrome undergoing induction, 36% of whom developed AKI.

Moreover, while the need for renal support therapy (RST) in itself represents an independent risk factor for a poor prognosis [6, 7], patients with HM who required RST in an intensive care unit (ICU) setting were reported to have higher mortality rates than those observed in general ICU patients also receiving RST [2].

The great majority of cancer patients developing AKI are usually managed by the attending physician. Yet, a small subgroup, mostly coincident with the worst presentation and prognosis, requires nephrology consultation and follow-up. These are often the patients that will challenge the clinician with ethical issues regarding the decision to initiate or forgo RST. Given the burden of the disease and the uncertainty of success, this is all too often a delicate task. Unfortunately, very little is available in the literature on the subject to help thoughtful decision making.

Accordingly, the present study aims to identify the prognostic determinants for in-hospital mortality in patients with HM and AKI.

Materials and methods

Design and data collection

A retrospective, observational chart review was undertaken at a single tertiary referral oncological centre. We reviewed the medical records of in-hospital patients with AKI and HM between 1 January 1995 and 31 December 2014, who met the criteria for RIFLE (Risk, Injury, and Failure; and Loss; and End-stage kidney disease) classification [8] of I or higher and were followed by a nephrologist. Data were collected based on records of the Nephrology Service of the hospital, which files all nephrology referrals. Laboratory and clinical information was then gathered from paper and electronic medical records. Classification of AKI according to the RIFLE criteria was assessed based on creatinine measurement and not on the glomerular filtration rate (GFR) as recommended by the last Kidney Disease: Improving Global Outcomes guidelines [9]. Urine output was not used since it was not available for all patients. Baseline creatinine was most often assessed by the lowest creatinine obtained during hospitalization or by earlier measurement. For patients with a previously normal renal function, we used creatinine determinations obtained at the latest 1 year before hospital admission; for patients with chronic renal disease, this was limited to the previous 3 months. For the very few cases where a baseline creatinine could not be measured, it was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation assuming that baseline GFR is 75 mL/min/1.73 m^2 [8, 10].

Patients had primary diagnosed, relapsed or refractory HM. Children ≥2 years of age were also included in the study. Those for whom palliative care was the only cancer treatment option were excluded.

Data collection included basic demographic details, type of tumour, treatment with stem cell transplantation (SCT), admission to the ICU, need for invasive mechanical ventilation (IMV), presence of septic shock, graft-versus-host disease (GVHD), characterization of AKI [prerenal (and if exclusively prerenal), obstructive, nephrotoxicity, hypercalcaemia, TLS, glomerulonephritis], need for RST and modality of RST. The different variables were accounted for if present at any time during hospitalization. Clinical outcomes were assessed as in-hospital death and were still included if patients were transferred to different departments.

Statistical analysis and prediction model

Univariate analyses were performed initially using the chi-square test to assess the relationship between each independent variable and mortality. Logistic regression was used to construct a model to predict mortality in the cohort. All variables that were significant on univariate analysis at $P < 0.20$ were included in the backward stepwise logistic regression model. Terms were removed from the model if the likelihood ratio statistics had a significance level >0.10 and terms were re-entered if the likelihood ratio statistic had a significance level <0.05.

Missing values were treated by list-wise deletion since the maximum percent missing was 0.9%.

Age was treated as a categorical variable, with cut-offs at 18 and 55 years, based on inspection of a locally weighted scatter plot curve [11]. Strong correlations between predictors were investigated to avoid multicollinearity. We undertook an a priori evaluation of several multiplicative interactions based on clinical grounds. Interaction terms were tested as candidate variables, but none of these terms entered the final model.

The quality of the logistic regression model was assessed in terms of discrimination and calibration. Discrimination was assessed by the area under the receiver operating characteristic (ROC) curve, the concordance index (C-statistic). The ROC curve was derived from predicted probabilities and a value >0.7 was considered to indicate sufficient predictive accuracy. The optimal cut-off value for sensitivity and specificity was determined by the Youden index J (sensitivity + specificity − 1) [12]. Calibration, the agreement between predicted and observed risk of death, was assessed by performing the Hosmer–Lemeshow goodness-of-fit test.

Because prediction models perform better in the development cohort than in other similar populations, an internal validation was performed using the bootstrap method to adjust for overoptimism [13]. The bootstrap procedure (500 draws with replacement) was applied to obtain parameter estimates for the C-statistic. Model optimism was subsequently assessed by comparing the bootstrap adjusted and the original model C-statistic.

Results

A total of 345 patients were included in the study. The median age was 51 (range 34–63) years and 60% were male. During the study period, 148 (43%) in-hospital deaths were reported.

The baseline characteristics are presented in Table 1. One hundred and thirty-seven patients needed SCT and 87% of them underwent allogeneic transplantation. Half (49.4%) of all the patients required RST.

The demographic and clinical characteristics were compared between survivors and non-survivors. The univariate analysis identified the following variables as significant predictive factors for in-hospital death: age (P = 0.013), SCT (P < 0.001), admission to ICU (P < 0.001), IMV (P < 0.001), septic shock (P < 0.001), nephrotoxicity (P = 0.004) and RST (P < 0.001).

Five factors provided protection against in-hospital death: exclusive prerenal AKI (p0 = 0.006), obstruction (P = 0.023), TLS (P = 0.011) and hypercalcaemia (P = 0.047). Survivors and non-survivors did not differ in gender, GVHD, glomerulonephritis and tumour type.

The results of the logistic regression analysis after backward selection are summarized in Table 2. The significant independent variables that remained predictors of in-hospital death after logistic regression were transplantation [allogeneic; odds ratio (OR) 2.23 (95% CI 1.26–3.95)], IMV [OR 4.31 (95% CI 2.08–8.93)] and septic shock [OR 4.29 (95% CI 2.06–8.94)].

Based on the above data and analyses, the β coefficients of the three variables were used to build a logistic regression equation and estimate the probability of in-hospital death:

$$p = \frac{1}{1+e^{-\beta}}, \text{ with } \beta$$
$$= -1.914 + 0.803 \times T1 + 0.545 \times T2 + 1.460 \times \text{IMV} + 1.456 \times \text{SS}$$

where $T1 = 1$ if allotransplantation
$T1 = 0$ if no allotransplantation
$T2 = 1$ if autotransplantation
$T2 = 0$ if no autotransplantation
IMV = 1 if mechanical ventilation
IMV = 0 if no mechanical ventilation
SS = 1 if septic shock
SS = 0 if no septic shock

The probability of in-hospital death for a given risk factor combination, based on logistic regression equation modelling, is shown in Table 3. For example, for a patient who was subject to allotransplantation, mechanical ventilation and had septic shock, the probability of in-hospital death was 85.9%.

According to the Hosmer–Lemeshow statistic, the reliability of the models was adequate (P = 0.505). Figure 1 presents the ROC curve drawn for the predicted probabilities of the logistic regression model, graphically depicting the ability of the model to discriminate between true cases and true non-cases. The C-statistic was 0.832 (95% CI 0.787–0.878), indicating that the equation with three variables had great discriminatory power. Based on the Youden index–optimized cut-off value of 0.55 (probability of in-hospital death 55%), the model had a sensitivity of 76.4% and a specificity of 83.8%. The C- statistic of the bootstrap model was 0.829. The average difference between the validated and bootstrapped sample (known as degree of optimism) was only 0.003.

Table 1. Characteristics of the study population

Characteristics	Survivors (*n* = 197)	Non-survivors (*n* = 148)	P-value	Overall (*N* = 345)
Age, years				
≤18	34 (17.3)	18 (12.2)	0.013	52 (15.1)
19–54	65 (33.0)	72 (48.6)		137 (39.7)
≥55	98 (49.7)	58 (39.2)		156 (45.2)
Gender				
Female	79 (40.1)	57 (38.5)	0.765	136 (39.4)
Male	118 (59.9)	91 (61.5)		209 (60.6)
Stem cell transplantation				
No	139 (70.6)	69 (46.6)	<0.001	208 (60.3)
Allo	50 (25.4)	69 (46.6)		119 (34.5)
Auto	8 (4.1)	10 (6.8)		18 (5.2)
Intensive care unit				
No	142 (72.1)	25 (16.9)	<0.001	167 (48.4)
Yes	55 (27.9)	123 (83.1)		178 (51.6)
Invasive mechanical ventilation				
No	159 (80.7)	36 (24.3)	<0.001	195 (56.5)
Yes	38 (19.3)	112 (75.7)		150 (43.5)
Septic shock				
No	163 (82.7)	39 (26.4)	<0.001	202 (58.6)
Yes	34 (17.3)	109 (73.6)		143 (41.4)
Graft-versus-host disease				
No	177 (89.8)	123 (83.1)	0.066	300 (87.0)
Yes	20 (10.2)	25 (16.9)		45 (13.0)
Acute kidney injury				
Exclusive prerenal[a]				
No	178 (90.8)	145 (98.0)	0.006	323 (93.9)
Yes	18 (9.2)	3 (2.0)		21 (6.1)
Obstructive[a]				
No	173 (88.3)	141 (95.3)	0.023	314 (91.3)
Yes	23 (11.7)	7 (4.7)		30 (8.7)
Nephrotoxicity[a]				
No	139 (70.9)	83 (56.1)	0.004	222 (64.5)
Yes	57 (29.1)	65 (43.9)		122 (35.5)
Tumoral lysis syndrome[a]				
No	171 (87.2)	141 (95.3)	0.011	312 (90.7)
Yes	25 (12.8)	7 (4.7)		32 (9.3)
Hypercalcaemia[a]				
No	179 (91.3)	143 (96.6)	0.047	322 (93.6)
Yes	17 (8.7)	5 (3.4)		22 (6.4)
Glomerulonephritis				
No	192 (97.5)	148 (100.0)	0.051	340 (98.6)
Yes	5 (2.5)	0 (0.0)		5 (1.4)
Renal support therapy[a]				
No	130 (66.7)	43 (29.3)	<0.001	173 (50.6)
HD	34 (17.4)	22 (15.0)		56 (16.4)
CVVH	21 (10.8)	70 (47.6)		91 (26.6)
HD and CVVH	10 (5.19)	12 (8.2)		22 (6.4)
Tumour type				
AML	30 (15.2)	34 (23.0)	0.010	64 (18.6)
ALL	34 (17.3)	30 (20.3)		64 (18.6)
NHL	63 (32.0)	44 (29.7)		107 (31.0)
MM	48 (24.4)	16 (10.8)		64 (18.6)
Others	22 (11.2)	24 (16.2)		46 (13.3)

HD, haemodialysis; CVVH, continuous venovenous hemofiltration; AML, acute myeloid leukaemia; ALL, acute lymphoid leukaemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma.
[a]Total *N* not equal to 345 due to missing values for some individual items. Values are *n* (%).

Discussion

The development of AKI often complicates the course of malignancies and is known to foretell a worse prognosis in an already frail population. When associated to other comorbidities and in a setting of severely ill patients, the indication for RST might be questionable given the high mortality rates, high costs and the

Table 2. Risk factors for in-hospital death in the final logistic regression model

Factors	β coefficient	P-value	OR (95% CI)
Stem cell transplantation			
No	Ref.	–	1
Allo	0.803	0.006	2.232 (1.260–3.953)
Auto	0.545	0.380	1.724 (0.511–5.819)
IMV			
No	Ref.	–	1
Yes	1.460	<0.001	4.305 (2.075–8.928)
Septic shock			
No	Ref.	–	1
Yes	1.456	<0.001	4.290 (2.058–8.943)

IMV, invasive mechanical ventilation.

Table 3. Probability of in-hospital death with and without each of the three risk factors

Allogeneic SCT	IMV	Septic shock	Probability of in-hospital death, %
No	No	No	12.9
Yes	No	No	24.8
No	Yes	No	38.8
No	No	Yes	38.7
Yes	Yes	No	58.6
Yes	No	Yes	58.5
No	Yes	Yes	73.1
Yes	Yes	Yes	85.9

SCT, stem cell transplantation; IMV, invasive mechanical ventilation.

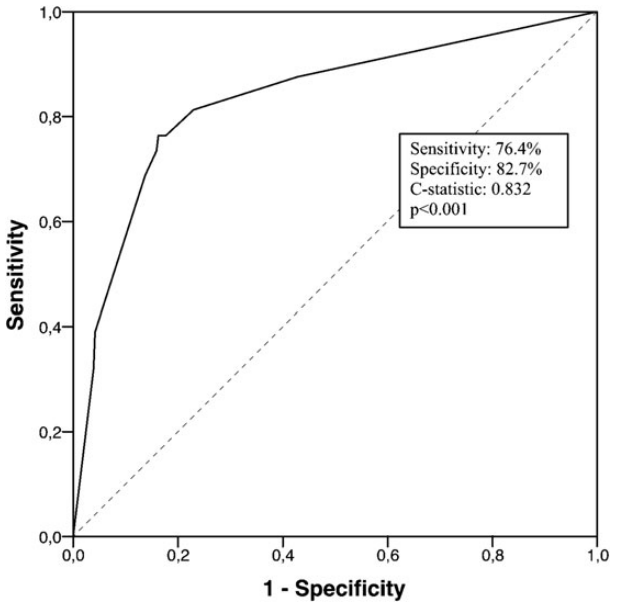

Fig. 1. Receiver operating characteristic curve to predict in-hospital death in patients with haematological malignancies who develop acute kidney injury.

suffering endured by the patients and their relatives [14, 15]. Unfortunately, very little has been published on the matter.

The present work aimed to determine which prognostic features of inpatients with HM and AKI were associated to a higher mortality.

The current study is, to the best of our knowledge, the only reported study to build a predictive model to help assess the prognosis of haematological patients who develop AKI and one of only a few studies addressing this subject.

Our findings revealed that patients with HM requiring nephrology consultation were more frequently male (60.6%), older patients (45.2% were >55 years old) with non-Hodgkin lymphoma (31%). The median age of our study population was comparable to previous studies. Canet *et al.* [3] reported the exact same median age of 51 years and Lahoti *et al.* [5] had a similar median age of 56 years. Some other works found slight differences, with Pène *et al.* [16] reporting a median age of 41 years and Benoit *et al.* [2] a median age of 62 years. On the one hand, these discrepancies probably depend on a different prevalence of the various haematological malignancies included, with some typically affecting younger patients, as is the case of acute lymphoblastic leukaemia, versus others with a higher incidence of older patients, such as multiple myeloma. On the other hand, different criteria for ICU admission or indication for more invasive treatment strategies might also make up for the different ages encountered.

Of the patients who had undergone SCT, 87% were submitted to allogeneic transplantation. This is not unexpected for two reasons: first, the absence of GVHD in autologous SCT, which can lead to renal lesion directly through cytokine and immune-related injury or indirectly through nephrotoxicity induced by cyclosporine used in prophylaxis against GVHD [17, 18]; second, because of the absence of foreign cells in myeloablative autologous SCT, engraftment occurs more rapidly (resulting in less cytopenia, sepsis and nephrotoxicity induced by antimicrobials) [19].

Among the aetiologies of AKI, nephrotoxicity was the most prevalent (35.5%), usually associated to antibiotics (vancomycin, aminoglycosides, quinolones, antifungals and antivirals) and less often to chemotherapy drugs, such as calcineurin inhibitors, cisplatin, methotrexate and ifosfamide. TLS (9.3%) and obstructive renal disease (8.7%) were also related to renal failure.

Our results are in agreement with previous works, which found a similar distribution of AKI risk factors [5, 20, 21]. However, our goal was not to determine nor characterize the incidence of AKI, but to identify which risk factors were more often related to fatal AKI. Altogether, the burden of nephrotoxic drugs remains one of the most consistent and worrisome findings in the literature because of the large number of patients affected.

Most of the patients were observed in the ICU setting (51.6%) and 49.4% of all the patients needed RST. Giving the fact that only patients with more serious AKI required nephrology observation, this did not surprise us.

Overall mortality was 43%. Soares *et al.* [22] found a greater mortality in their analysis (64% overall hospital mortality), but his cohort study was conducted solely in ICU patients, who were predictably more unstable, and included both solid tumours and haematologic malignancies. Similarly, correlations to other previous studies are difficult to establish since most of them evaluated very specific populations, usually in ICU settings, and often handled patients with different malignant diseases [2, 5, 16, 23].

In our study, we found that the aetiology of AKI and, ultimately, the conjugation of its different determinants has a great effect on the patients' prognosis and should prompt the clinician's decision regarding the approach and follow-up of each situation.

A prediction model based on multivariate logistic regression analysis was developed with in-hospital death as the outcome. The model showed overall good discrimination in identifying

patients at risk. Our investigation was able to determine which conditions were linked to increased mortality and how the combination of each risk factor influenced the final prognosis: our findings revealed that the association of IMV, septic shock and allogeneic SCT entail the greatest risk of in-hospital death (86%).

The latter two are often markers of a pronounced severity of illness and great susceptibility and were significantly correlated to a worse prognosis in the works of Lahoti *et al.* [5], Benoit *et al.* [2] and Soares *et al.* [22]. Pène *et al.* [16] and Lopes *et al.* [24] highlighted the bad prognosis of allogeneic SCT in the context of severely ill patients. These have increased mortality due to several mechanisms, including volume overload, coagulation abnormalities, an increased incidence of sepsis with multiorgan failure and cytokine or immune-mediated major organ dysfunction.

With regard to IMV, Lahoti *et al.* also suggested a relationship between the need for invasive ventilation and the presence of overhydration, which often occurs during chemotherapy and is, *per se*, associated with increased mortality in various clinical settings [25–27].

Consequently, we were able to deliver individualized predictions and identify which subgroup of patients would be more likely to benefit from treatment and those for whom the indication for aggressive life support might represent a hopeless and futile effort and suffering. Nevertheless, we recognize that each patient merits careful consideration and that, should there be uncertainty regarding the outcome, RST should be tried.

Importantly, our findings suggest that the presence of an HM, by itself, should not be a reason to withhold RST, although the overall prognosis is poor and limited by that of the underlying disease and comorbidities.

There are some limitations to the current study. First, this was a retrospective cohort collected in a single centre without external validation. However, the overfitting was addressed by using the bootstrap method. Second, extrapolation of the data needs to take into account the restriction to the particular population included in the study, namely patients with HM with moderate to severe AKI who are receiving treatment with curative intent.

Third, different stages of HM were included and we did not account for cancer remission. Hence, the outcomes might be influenced by the underlying cancer status, since it is well known that the patients who fail to achieve a complete remission have a worse prognosis [5].

Last, we used a broad time span, along which the management of oncologic diseases, mainly related to the introduction of target therapies, might have changed, and this could render the patients less comparable.

In conclusion, this retrospective cohort study suggests that patients with HM and AKI, despite widely considered as poor candidates for RST, should not, a priori, be excluded from such support therapies. They should instead be approached with careful interpretation of a combination of risk factors. Our work found that the association of mechanical ventilation, septic shock and allogeneic STC is indicative of a very high risk of in-hospital death. The use of the prediction model may facilitate the identification of patients with the greatest mortality risk and help clinicians in the decision-making process.

In addition, knowledge of the factors that contribute significantly to a worse prognosis is crucial to identify where to focus clinical and research efforts in order to contribute to reduction of the case fatality rate.

Further research should be undertaken to validate our predicted model in independent populations and extend its application to a wider spectrum of patients.

Conflict of interest statement

There are no conflicts of interest to declare. The authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

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