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ORIGINAL ARTICLE

Renal recovery after severe acute kidney injury in critically ill myeloma patients: a retrospective study

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Abstract

Background: Despite substantial improvements in the management of multiple myeloma, renal failure remains an important burden that tremendously impairs prognosis. The purpose of this study was to describe the characteristics and to establish prognostic factors of renal recovery in myeloma patients admitted to the intensive care unit (ICU) for acute kidney injury (AKI) Stage 3 treated with renal replacement therapy (RRT).

Methods: A retrospective single-centre cohort study was performed, including consecutive myeloma patients admitted to one medical ICU between 1 January 2007 and 1 September 2015 and treated with RRT. Patients were evaluated 60 days after initiation of RRT and divided into three groups: alive without dialysis, alive and dialysis-dependent or deceased. A univariate analysis was performed to identify factors associated with renal recovery (alive without dialysis 60 days after initiation of RRT).

Results: Fifty patients were included in the study. Mean age was 63 (interquartile range: 58–70) years and 32 (64%) were male. Patients were admitted to the ICU 4 (1–7) years after the diagnosis of myeloma. Twenty-one (42%) had already been treated with high-dose therapy combined with autologous stem cell transplantation. Baseline renal function evaluated by estimated glomerular filtration rate (GFR) before ICU admission was 63 (44–90) mL/min/1.73 m^2. The mean SOFA score at Day 1 was 7 (4–8). The three main reasons for ICU admission were AKI ($n = 31$, 62%), acute pulmonary oedema ($n = 17$, 32%) and sepsis ($n = 10$, 20%). During ICU stay, RRT was implemented in all patients, 16 (32%) patients required invasive mechanical ventilation and 12 (24%) received vasopressors. The mean ICU and hospital length of stay were 6 (1–7) and 28 (13–34) days, respectively. At Day 60, 23 (46%) patients were alive without dialysis, 17 (32%) had died and 10 (20%) were still undergoing dialysis. Among the 23 patients who recovered, the mean duration of dialysis was 6 (2–18) days and renal function was not significantly different from baseline [estimated GFR at baseline = 65 (25–74) mL/min/1.73 m^2 versus 63 (56–70) mL/min/1.73 m^2 at Day 60, $P = 0.70$]. By univariate analysis, two factors were associated with nonrecovery of renal function at Day 60: a history of high-dose therapy combined with autologous stem cell transplantation [odds ratio (OR) = 6.1, 95% confidence interval (CI) 1.7–21.6; $P = 0.008$] and a proteinuria at ICU admission >370 mg/mmol creatinine (OR = 4.2, 95% CI 1.1–17;

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P = 0.02). None of the other variables related to the haematological malignancy or to the ICU stay was associated with renal recovery at Day 60.

Conclusions: AKI Stage 3 in critically ill myeloma patients was associated with a lower than expected hospital mortality. Patients with a high level of proteinuria and a history of high-dose therapy combined with autologous stem cell transplantation were less likely to recover their renal function at Day 60.

Key words: dialysis, intensive care, multiple myeloma, prognosis, proteinuria

Introduction

Myeloma is the second most common haematological malignancy [1] and remains the first neoplasm responsible for end-stage renal disease [2].

Despite substantial improvements in its management, renal failure occurs in up to 50% of patients [with 10% needing renal replacement therapy (RRT)] [3] and tremendously impairs prognosis, with a median survival of 3.5–10 months [4] for those under dialysis. Reversibility of renal failure can improve this otherwise grim prognosis [3].

Therefore, the question of recovery is crucial in the management of acute kidney injury (AKI) requiring dialysis and in the course of myeloma.

More than 10% of myeloma patients [5] will require intensive care unit (ICU) admission, mostly for AKI (39–51%, 24–44% of which needing RRT) [6].

Rates of renal recovery are largely variable, ranging from 17% [4] to 75% [7] in recent trials, but to our knowledge no previous study has evaluated the prognosis of AKI in myeloma patients specifically in the ICU setting.

The purpose of this study was to describe the impact of severe AKI on both a patient's and kidney's prognosis in critically ill myeloma patients and to identify factors associated with renal recovery after initiation of RRT.

Materials and methods

We performed a retrospective cohort study including consecutive myeloma patients admitted to the medical ICU of St Louis University Hospital, Paris, France (a 650-bed hospital with 330 beds dedicated to haematology and oncology) between 1 January 2007 and 1 September 2015 and treated by RRT throughout the ICU stay. Medical records were reviewed and screened for variables of interest.

Inclusion criteria were as follows:

(i) multiple myeloma diagnosis according to the International Myeloma Working Group diagnostic criteria [8]

(ii) severe AKI, defined as Stage 3 of the Kidney Disease: Improving Global Outcomes criteria (i.e. three times baseline increase in serum creatinine or increase in serum creatinine to $\geq$ 4.0 mg/dL or urine output of $<$ 0.3 mL/kg/h for $\geq$24 h or anuria for $\geq$12 h) treated by RRT [9]

(iii) baseline glomerular filtration rate (GFR) $>$15 mL/min/1.73 m^2.

Patients with amyloidosis or light-chain deposition disease (LCDD) were excluded, so that proteinuria, if present, was exclusively composed of free light chains (FLC). Proteinuria was considered significant if $>$50 mg/mmol.

Data were abstracted from the medical charts and we included variables related to the ICU stay (Sequential Organe Failure Assessment (SOFA) at Day 1, Simplified Acute Physiology Score II (SAPS II), use of vasopressors or mechanical ventilation, continuous or intermittent dialysis), the myeloma characteristics before (time from diagnosis, treatments received, baseline renal function and disease activity according to the International Myeloma Working Group definition [10]) and at the time of AKI (serum free light chains, serum peak immunoglobulin), and the follow-up after ICU discharge (length of dialysis maintenance therapy, response to treatment and vital status). Baseline renal function was defined as the best renal function in the month before ICU admission, using the CKD-EPI (Chronic Kidney Disease - Epidemiology Collaboration) equation.

Outcome was collected 60 days after RRT implementation. Recovery group was defined as patients alive and free of dialysis and nonrecovery as a composite endpoint of death and dialysis dependence, as advocated by the National Institute of Diabetes, Digestive and Kidney Diseases [11]. Admissions were divided between 2007–11 and 2012–15, which corresponds to the middle of the study period and to the authorization of SC bortezomib by the European Medicines Agency (2012), to assess for improvement of overall prognosis.

Baseline and follow-up characteristics were described by means and standard deviation (SD), SD or interquartile range (IQR) for continuous variables normally distributed or with skewed distribution, respectively, and by percentages for categorical variables. Proteinuria was divided according to the median value in our sample to take into account the supersaturation phenomenon that occurs in urine.

Characteristics between recovery and nonrecovery groups were compared using Mann–Whitney test for continuous data and Fisher's exact test for categorical data.

All tests were two-sided, and $P < 0.05$ were considered statistically significant. Analyses were done using the Statview 5.0 software package (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 50 patients were included in the study. One was lost to follow-up at Day 60. Patients' characteristics are described in Table 1.

Mean age was 63 (IQR: 58–70) years and 32 (64%) were male.

Patients were admitted into the ICU 4 (0.8–5.3) years after the diagnosis of myeloma, after two (one to three) lines of chemotherapy.

Bence Jones proteinuria was noted at ICU admission in 35 (70%) cases. Six patients had proteinuria of other or unknown origin and among them only one had predominant albuminuria (96 mg/mmol). Nine patients had other causes of AKI (hypercalcaemia, sepsis, dehydration, nephrotoxic drugs, etc.) without significant proteinuria ($<$50 mg/mmol).

Among those (n = 35) with presumed myeloma cast nephropathy, a superimposed triggering event was identified in 18

Table 1. Characteristics of patients included ($n = 50$)

Demographic and clinical data for all patients ($n = 50$)	
Age [mean (IQR)] (years)	62.6 (58–70)
Male sex, *n* (%)	32 (64)
Time from myeloma diagnosis to ICU admission [mean (IQR)] (years)	4 (0.8–5.3)
Myeloma status at ICU admission, *n* (%)	
Newly diagnosed	19 (38)
Partial response	1 (2)
Stable disease	2 (4)
Relapse	19 (38)
Progressive disease	9 (18)
Number of lines of chemotherapy prior to ICU admission [mean (IQR)]	2 (1–3)
Chemotherapy received prior to admission, *n* (%)	
Bortezomib	34 (68)
Cyclophosphamide	26 (52)
Melphalan	27 (54)
Thalidomide	25 (50)
Corticosteroids	33 (66)
None	4 (8)
Chemotherapy at the time of admission, *n* (%)	
Bortezomib	22 (44)
Cyclophosphamide	10 (20)
Melphalan	6 (12)
Thalidomide	9 (18)
Revlimid	7 (14)
Corticosteroids	24 (48)
None	9 (18)
High-dose therapy combined with autologous stem cell transplantation, *n* (%)	21 (42)
SOFA score at Day 1 (mean + IQR)	7 (4–8)
SAPS II [mean (IQR)]	53 (40–63)
Reason for ICU admission, *n* (%)	
Renal failure	31 (62)
Respiratory failure	10 (20)
Cardiac failure	3 (6)
Coma	3 (6)
Other	3 (6)
Aplasia, *n* (%)	4 (8)
RRT	50 (100)
Length of RRT [mean (IQR)] (days)	7.5 (4–41)
Noninvasive ventilation, *n* (%)	5 (10)
Mechanical ventilation, *n* (%)	16 (32)
Vasopressors, *n* (%)	12 (24)
ICU length of stay [mean (IQR)] (days)	6 (1–7)
Hospital length of stay [mean (IQR)] (days)	28 (13–34)
Laboratory data	
Type of paraprotein, *n* (%)	
IgG	27 (54)
IgA	12 (24)
IgD	1 (2)
Light chain, *n* (%)	
Kappa	32 (64)
Lambda	20 (36)
Light chain only, *n* (%)	10 (20)
Kappa	8 (80)
Lambda	2 (20)
Proteinuria [mean (IQR)] (mg/mmol creatinine)	393 (84–557)
Bence Jones proteinuria, *n* (%)	35 (70)
Baseline GFR [mean (IQR)] (mL/min/1.73 m^2)	63 (44–90)
Albuminemia [mean (IQR)] (g/L)	31.6 (26.0–36.0)
Monoclonal peak [mean (IQR)] (g/L)	18.0 (1.2–33.9)
Calcaemia [mean (IQR)] (mmol/L)	2.56 (2.47–2.65)

(51%) cases: dehydration in 7 [diarrhoea or vomiting ($n = 5$), haemorrhage ($n = 2$)], sepsis in 5, exposure to nephrotoxic drugs in 5 [iodinated contrast product ($n = 5$), Non-steroidal anti-inflammatory drugs (NSAIDs) ($n = 3$)] and hypercalcaemia in 1 patient.

Myeloma was newly diagnosed for 19 (38%) patients and relapsing for 19 (38%).

Other patients had partial response ($n = 1$, 2%), stable ($n = 2$, 4%) or progressive ($n = 9$, 18%) disease. None was considered in good or very good response at the time of AKI diagnosis.

Most often received chemotherapeutic drugs prior to ICU admission were: bortezomib (34, 68%), cyclophosphamide (26, 52%), melphalan (27, 54%) and thalidomide (25, 50%). Four patients had never been treated and received their first chemotherapy in the ICU. At the time of admission, 22 patients (44%) were receiving bortezomib, 10 (22%) cyclophosphamide, 9 (18%) thalidomide and 9 (18%) were not currently treated.

Twenty-one (42%) patients had already been treated with high-dose therapy combined with autologous stem cell transplantation (HDT-ASCT) 3 years (1–5) before ICU admission, including four patients treated 2, 10, 10 and 16 days before admission.

Baseline renal function before ICU admission, estimated by the CKD-EPI GFR, was 63 (44–90) mL/min/1.73 m^2. The mean SOFA score at Day 1 was 6.6 (4–8) and the three main reasons for ICU admission were AKI ($n = 31$, 62%), acute pulmonary oedema ($n = 17$, 32%) and sepsis ($n = 10$, 20%). During ICU stay, RRT was implemented in all patients [continuous veno-venous haemofiltration for 5 (10%) patients], 16 (32%) patients required invasive mechanical ventilation and 12 (26%) received vasopressors. The mean ICU and hospital length of stay were 6 (1–7) and 28 (13–34) days, respectively.

Outcome

Outcomes are described in Figure 1: 60 days after initiation of RRT, 23 (46%) patients were alive without dialysis, 17 (34%) had died and 10 (20%) were still under RRT. Among the 23 patients who recovered, the mean time of dialysis was 6 (2–18) days. Mean GFR at Day 60 in the recovery group was 65 (25–74) mL/min/1.73 m^2, which was not statistically different from baseline ($P = 0.70$).

Comparison between recovery and nonrecovery groups)

In univariate analysis, two factors were associated with a decreased likelihood of renal recovery at Day 60 (Tables 2 and 3): a history of HDT-ASCT [odds ratio (OR) 6.1, 95% confidence interval (CI) 1.7–21.6; $P < 0.01$] and a proteinuria at ICU admission >370 mg/mmol creatinine (OR = 4.2, 95% CI 1.1–17; $P = 0.02$).

There was a nonstatistically significant trend toward lower monoclonal spike (24.5 versus 13.7 g/L, $P = 0.15$) and less use of bortezomib (OR = 4, 95% CI 1.1–14.4; $P = 0.06$) in the nonrecovery group.

Age (65.5 versus 60.5 years, $P = 0.10$), time from diagnosis (4.6 versus 3.5, $P = 0.98$), SOFA score at Day 1 (6.9 versus 6.6, $P = 0.59$) and baseline GFR (58.2 versus 66.2 mL/min/1.73 m^2, $P = 0.37$) were not different between the two groups. Neither were calcaemia, exposition to nephrotoxic drugs (NSAIDs, iodinated contrast products, angiotensin-converting enzyme inhibitors or aminoglycosides), use of vasopressors or preserved diuresis (all $P > 0.05$). The serum free light chain was available in 27 (55%) patients and was not associated with recovery, using the median FLC level in our sample as a threshold ($P > 0.45$).

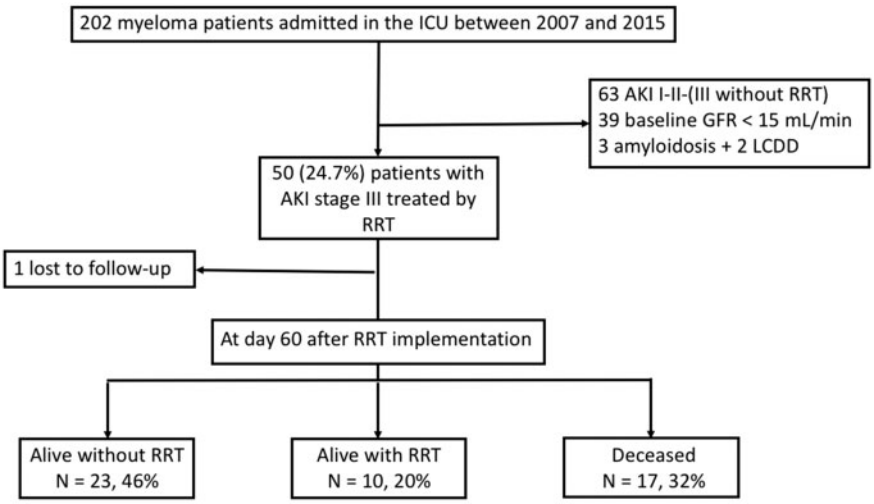

Fig. 1. Flow chart and outcomes of patients admitted for Stage 3 AKI and need for RRT.

Table 2. Comparison between recovery and nonrecovery groups for continuous variables

	Recovery ($n = 23$)	Nonrecovery ($n = 27$)	P-value
Age (years)	65.5 (58.0–70.7)	60.5 (55.2–67.4)	0.10
Time from myeloma diagnosis (years)	4.6 (2.4–6.9)	3.5 (1.5–5.5)	0.98
SOFA score at Day 1	6.9 (4.3–8.8)	6.6 (4.5–7.5)	0.59
SAPS II score	52.6 (40.0–61.3)	53.7 (40.5–63.5)	0.94
Baseline GFR (mL/min/1.73 m^2)	58.2 (47–65)	66.2 (44–96)	0.37
Monoclonal spike (g/L)	24.5 (1.6–40.8)	13.7 (1.1–24.5)	0.15
Serum albumin (g/L)	32.1 (26.3–37)	31.3 (27–36)	0.67
Calcemia (mmol/L)	2.62 (2.3–2.8)	2.47 (2.2–2.5)	0.12

Data are presented as means (IQR).
P-values were calculated using the MannWhitney test.

Table 3. Comparison between recovery and nonrecovery groups for categorical variables

	Recovery ($n = 23$) n (%)	Nonrecovery ($n = 27$) n (%)	OR (95% CI)	P-value
Mechanical ventilation	7 (30.4)	9 (33.3)	1.1 (0.4–3.8)	0.83
Vasopressor drugs	3 (13.0)	9 (33.3)	3.3 (0.6–19.2)	0.09
Proteinuria >370 mg/mmol	7 (30.4)	18 (81.5)	4.2 (1.1–17)	0.02
Nephrotoxic drug exposure	15 (65.2)	15 (55.6)	0.7 (0.2–2.1)	0.49
Iodinated contrast exposure	0 (0)	5 (18.5)	11.5 (0.6–220)	0.09
Preserved diuresis	10 (43.5)	8 (29.6)	0.6 (0.2–1.8)	0.31
Serum free light chain >5000 mg/L	2 (8.7)	5 (18.5)	2.4 (0.4–13.7)	0.56
HDT-ASCT	4 (17.4)	17 (63.0)	6.1 (1.7–21.6)	0.01
Bortezomib	12 (52.2)	22 (81.5)	4 (1.1–14.4)	0.06
Admission between 2007 and 2011	12 (52.2)	16 (59.3)	1.3 (0.4–4.1)	0.62

Notably, none of the five patients who received iodinated contrast products recovered.

There was no significative trend over time for renal recovery (2007–11: 46% versus 2012–15: 48%, P = 0.62). There was no influence of primary admission diagnosis on renal recovery (renal failure versus others, P = 0.75).

In *post hoc* analysis, we found that a history of HDT-ASCT drove the association with increased mortality (OR = 4, 95% CI 1.2–14, P = 0.02) but was not associated with dialysis dependency at Day 60 (P = 0.12).

Among the 33 patients alive at Day 60, 2 required haemodialysis 9 and 29 months after ICU admission, while 2 patients treated by RRT at Day 60 recovered 2.3 and 3.5 months later.

The mean follow-up for these 33 patients was 20 months and for the 12 who died before the end of follow-up, the mean overall survival time was 19 months.

During the same period, 21 myeloma patients underwent RRT without being admitted in the ICU: 11 for end-stage renal disease, 8 for AKI and 2 with unknown baseline renal function who underwent RRT since the diagnosis of multiple myeloma and did not recover. Among the eight AKI patients not admitted in the ICU, at Day 60, four were still undergoing RRT, three were alive without dialysis and one was deceased. The characteristics of these patients (age, number of previous treatments, history of stem cell transplantation) did not differ from those admitted in the ICU.

Discussion

In this study, 32% of multiple myeloma patients admitted in the ICU and treated with RRT finally died while 41% recovered their renal function 60 days after initiation of RRT, without a significant decrease in renal function. Proteinuria >370 mg/mmol creatinine and a history of HDT-ASCT were associated with nonrecovery of renal function.

This study is the first to assess renal recovery in critically ill myeloma patients with severe AKI, in the era of novel therapies such as bortezomib, lenalidomide and thalidomide.

Studies from the late 1990s reported rates of renal recovery as low as 8% [12] to 15% [13] for patients undergoing dialysis, painting a bleak picture of myeloma patients requiring RRT and promoting a nihilistic attitude toward their ICU admission.

With the advent of novel agents' induction therapies, recent studies have spread hope of improving these patients' outcome with rates of recovery as high as 75% and survival improving from 18 to 32 months in the most recent studies [14].

First of all, our study describes rates of survival and renal recovery higher than previously reported, with 46% of the patients alive and free of dialysis at Day 60.

Interestingly, we identified that prognostic factors of renal recovery were largely independent of classic intensive care variables, but instead relied on tumour burden and haematological prognostic factors.

History of HDT-ASCT was unexpectedly associated with poor renal recovery. This might be explained by severity of AKI occurring in this setting (which was the case for four patients who were hospitalized shortly after graft infusion), and patients with uncontrolled disease who were in relapse after the ASCT procedure. Although previous studies have reported that the haematological prognosis usually does not or marginally influence the prognosis in the ICU [15], our experience with a targeted population of critically ill myeloma patients with severe AKI was different. This might be explained by the fact that the main organ dysfunction in our study (AKI) was closely linked to the underlying disease activity.

Notably, the association between HDT-ASCT and nonrecovery remained significant if we excluded the four patients who were admitted during engraftment.

Proteinuria was mainly constitutive of monoclonal light chains, as patients diagnosed with amyloidosis or LCDD were excluded, and only four patients had proteinuria composed of <50% monoclonal light chains. Therefore, albuminuria was unlikely to influence results concerning prognostic value of proteinuria.

The time of ICU admission (2007–11 versus 2012–15) had no influence on renal recovery, despite several improvements in myeloma and AKI care in general. This lack of improvement may be explained by the limited number of patients included in the present study and by a broader ICU admission policy of myeloma patients in the ICU.

Previous studies reported age and baseline renal function as determinants of recovery after AKI [16, 17] in the overall population. In our study, homogeneity in age probably prevented any difference from appearing, but baseline GFR, provided that statistical power was sufficient, did not seem to be associated with recovery in the context of myeloma. The specific mechanisms of aggression of myeloma-related AKI, largely independent of baseline renal function, probably account for this finding. Indeed, precipitation of light chains largely depends on their tubular concentration, which is expected to be affected marginally by GFR (in favour of higher tubular concentration in the best baseline renal function) but mostly from diuresis and tumour load.

Indeed, renal prognosis of myeloma patients in the ICU setting has not been assessed yet, while studies conducted outside the ICU pointed to proteinuria and calcaemia [12] as prognostic factors of recovery from AKI. If our study confirmed proteinuria as an important prognostic factor, it does not support a role for hypercalcaemia, which may be related to the introduction of bisphosphonate therapy (six patients in our study received bisphosphonate during their hospitalization) in comparison with older studies.

Decisions regarding admission or limitation of the therapeutic efforts should take into account these results, and we hope this study, along with others describing an improved overall and intensive care prognosis of myeloma patients [6, 14], will encourage discussion between haematologists, renal and intensive care physicians and aid decision-making in clinical practice.

Our study also has several limitations. Statistical power was limited by a small number of cases and some missing data, probably preventing several intuitive factors (e.g. monoclonal peak, serum free light chain excess) from becoming statistically significant. Serum free light chain was obtained in only 55% of patients. This may be due in part to the time frame of the study (2007–15) but precludes any definitive conclusion upon the prognostic value of their measurement. Proteinuria was a significant prognostic factor only when considered as a categorical variable, probably due to a supersaturation phenomenon defining a risk threshold. The strength of the association and the intuitive plausible mechanism make a statistical artifact very unlikely. The usual caveats of a retrospective single centre study, such as recruitment bias or standardization of practice, also apply and should be taken into account. A recruitment bias is unlikely, as most patients with AKI requiring RRT were admitted in the ICU and the patients who were not admitted do not appear different in terms of initial characteristics or outcome.

Moreover, patients' characteristics were inhomogeneous, representing several disease stages and degrees of severity (e.g. 38% initial diagnosis of myeloma versus 38% relapse). Instead of representing a bias, we believe this pragmatic approach allows us to draw conclusions about a broad range of myeloma patients admitted in the ICU.

Renal recovery after AKI is an area of active research, and defining renal recovery has been controversial [11].

In our study, we used an endpoint that combines survival and dialysis independency at Day 60, as advocated by the National Institue of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop on trial methodology [18]. One could argue that results could have been driven by only one of these two factors. In this sense, we saw in supplementary analyses that a history of HDT-ASCT was more associated with survival. Nevertheless, we think that, apart from allowing a higher number of patients in each group and reducing the number of analyses, this definition of recovery is more relevant to clinical practice, as it combines two important goals in the care of myeloma patients on RRT.

Importantly, data concerning survival and recovery of renal function was obtained in nearly all patients (one patient was lost to follow-up while still under dialysis after Day 30).

Conclusion

AKI Stage 3 in critically ill myeloma patients was associated with lower hospital mortality and higher rate of renal recovery than previously described. Renal recovery is inversely associated with more aggressive malignancies, with a higher level of proteinuria and a history of HDT-ASCT being risk factors for death or dialysis dependence. These results can influence the decision to admit myeloma patients in the ICU for RRT and provide a support for discussion between haematologists, renal and intensive care physicians.

Conflict of interest statement

None declared.

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