Renal outcomes in myeloma associated acute kidney injury; a single centre experience

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ABSTRACT

Introduction: At initial diagnosis of multiple myeloma (MM) 30% to 40% of patients has renal impairment and acute kidney injury (AKI) being most common renal presentation. Poor renal outcome is associated with poor overall survival of patients.

Objectives: The present study was conducted to determine renal outcome in patients with newly diagnosed MM presenting with AKI.

Patients and Methods: A prospective observational study was carried out from March 2016 to March 2021. We included newly diagnosed myeloma patients presenting with AKI. Diagnosis and staging of AKI was conducted by kidney disease improving global outcomes (KDIGO) guidelines. Diagnosis of MM was performed by International Myeloma Working Group (IMWG) criteria. Complete renal response was defined as estimated glomerular filtration rate (eGFR) of ≥60 mL/min. Statistical analysis was done using SPSS Statistics software version 28.

Results: Total number of patients were 48 male, female was 32.16, median age was 69 years. With a median follow-up of 9 weeks 30 patients (62.5%) had complete renal response, 10 patients (20.8%) expired and 8 patients (16.6%) were dialysis dependent. On comparing patients with and without complete renal response, significant variables were serum creatinine (P < 0.001), serum calcium (P < 0.001), oliguria at presentation (P < 0.001), RRT requirement (P < 0.001), AKI stage III (P < 0.001) and light chain myeloma (P < 0.001). On Kaplan Meier analysis oliguria at presentation (P < 0.001), renal replacement therapy (RRT) requirement (P < 0.001), AKI stage III (P < 0.001) and light chain myeloma (P < 0.001) were significantly associated with poor renal outcomes.

Conclusion: In patients with newly diagnosed MM presenting with AKI renal recovery is 62.5%. Factors associated with poor renal recovery are higher serum creatinine, oliguria, RRT requirement, AKI stage III and light chain myeloma.

Keywords: Myeloma kidney, Multiple myeloma, Acute kidney injury, Renal outcome

Impact for health policy/practice/research/medical education:

In this prospective observational study of 48 newly diagnosed myeloma patients with AKI we found a renal recovery of 62.5%. Presence of higher serum creatinine, oliguria, renal replacement therapy requirement, AKI stage III and light chain myeloma were associated with poor renal recovery.

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Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder. Incidence of MM in India is 1.27 per lakh population with higher incidence in males (1). Age group in MM varies with geographic region of India, with northern and central zones has higher proportion in the 50-59 years age group, whereas eastern zone has higher proportion in aged 70 years and above (1) At initial diagnosis of MM, 30% to 40% of patients has renal impairment (2) and acute kidney injury (AKI) being most common renal presentation (3). Around 10% of patients with severe renal impairment will be dialysis dependent (2).

Myeloma cast nephropathy (MCN) is the most common cause of kidney disease in MM patients (3). MCN was present in 86.6% of the patients with severe AKI (4). Around 50 % to 60% of MM patients with renal impairment have complete renal recovery (5) and overall survival of MM patients is related with the extent of renal recovery (5,6). With the introduction of bortezomib based chemotherapy there is improved overall survival and renal function in MM (7).

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Objectives
The present study was carried out to determine renal outcome and factors associated with renal recovery in patients with newly diagnosed MM presenting with AKI.

Patients and Methods

Study design
It is a prospective observational study. Study period from March 2016 to March 2021. We included newly diagnosed myeloma patients presenting with AKI. Myeloma patients with chronic kidney disease (CKD) or nephrotic syndrome, the previously treated myeloma patients, lost follow-up cases and individuals not consenting for study were excluded. Consent from study participants and institutional ethics committee approval was taken.

Clinico-epidemiological data was documented in all patients. They included; complete blood count, renal function test, total protein, serum albumin, serum electrolytes - Na, K, Cl, Ca++, abdominal ultrasound, urine analysis, 24 hours urinary protein, urine for Bence Jones protein, peripheral blood smear, skeletal survey of axial skeleton, bone marrow aspiration, serum electrophoresis, urine electrophoresis, serum β2 microglobulin, serum immunoglobulin and serum free light chain (FLC) assays. Renal biopsy was considered if there was evidence of albuminuria by dipstick analysis or serum FLC <500 mg/L (8).

Diagnosis and staging of AKI was conducted as per KDIGO guidelines (9). Diagnosis of MM was done as per International Myeloma Working Group (IMWG) Criteria with evidence of bone marrow ≥10% plasma cells and myeloma defining events (10). Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease equation. Complete renal response was defined as eGFR of ≥60 mL/min (8).

Patients treated with bortezomib based chemotherapy (weekly-injection bortezomib 2 mg subcutaneous and oral dexamethasone 40 mg and daily Tab thalidomide 200 mg). Complete blood count and renal function test was monitored every week. Patients were followed-up for a period of 12 weeks or death or complete renal response whichever is earlier.

Statistical analysis
Statistical analysis was conducted using SPSS Statistics software version 28.0.0.0 (190). Continuous variables are expressed in mean ± SD and compared using student’s t test. Categorical variables are expressed as percentage and compared applying chi-square test. Time to event (complete renal response) was analysed by Kaplan-Meier analysis with log rank test for comparison. \( P \) value < 0.05 is considered statistically significant.

Results
Total number of patients included in the study was 48 cases with 32 males. Median age was 69 years (range 51 years to 78 years). Ten patients were <60 years and 38 patients were ≥ 60years respectively. Clinical features of study population are shown in Figure 1. Around 46 patients had anemia, 18 patients had hypercalcemia, 28 patients had monoclonal band in serum, 22 patients had monoclonal band in urine, 16 patients had monoclonal band in serum and urine, 20 patients had evidence of osteolytic lesion, 28 patients had Bence Jones proteinuria, albumin/globulin (A/G) ratio reversal and bone marrow ≥ 10% plasma cells was present in all 48 patients. Twenty-two patients had oliguria at presentation and 16 required RRT at presentation. Precipitating factors for AKI was found in 30 patients. Moreover, 18 patients had hypercalcemia, two had prior non-steroidal anti-inflammatory drugs use,

Figure 1. Clinical features of study population (X axis: number of patients, M band: Monoclonal band, Hypercalcemia: Serum corrected calcium ≥11 mg/dL, anemia: Hemoglobin <10 g/dL).
two diuretics and eight patients had infection, six had urinary tract infection and two had lower respiratory tract infection. There were six patients in AKI stage I, 20 in AKI stage II and 22 in AKI stage III respectively (Figure 2). IgG kappa myeloma was most common type with 32 patients, eight patients had IgA kappa and 8 had kappa light chain myeloma (Figure 3). Renal biopsy was conducted in seven patients. Accordingly, four patients had rapidly progressive renal failure (RPRF) presentation, showed MCN with significant interstitial inflammation on biopsy and all four patients had kappa light chain myeloma.

Besides three patients had albuminuria, on biopsy showed MCN with interstitial inflammation and background diabetic nephropathy.

About 42 patients received bortezomib based chemotherapy. Six patients had severe infection died before initiation of chemotherapy, while two patients developed leukopenia no other serious adverse effects were seen with chemotherapy. With a median follow-up of 9 weeks 30 patients (62.5%) had complete renal response, ten patients (20.8%) expired and eight patients (16.6%) were dialysis dependent (Figure 4). To compare patients with and without complete renal response, significant variables were, serum creatinine ($P<0.001$), serum calcium ($P<0.001$), oliguria at presentation ($P<0.001$), RRT requirement ($P<0.001$), AKI stage III ($P<0.001$), and light chain myeloma ($P<0.001$; Table 1). On Kaplan Meier analysis oliguria at presentation (log rank $P<0.001$), RRT requirement (log rank $P<0.001$), AKI stage III (log rank $P<0.001$), and light chain myeloma (log rank $P<0.001$) were significantly associated with poor renal outcomes (Figure 5).

**Discussion**

The present study was conducted to determine renal outcome in patients with newly diagnosed MM presenting with AKI. In our study 10 patients (20.8%) were <60 years and 38 patients (79.2%) were >60 years, this finding is similar with previously published studies MM affects middle and elderly age groups (11-14). In our study of 48 MM patients with AKI, 46 (95.6%) had anemia, 18 (37.5%) had hypercalcemia, 28 (58.4%) had M-band in serum, 22 (45.8%) had M-band in urine, 16 (33.3%) had M-band in serum and urine, 20 (41.6%) had evidence of osteolytic lesion, 28 (58.4%) had Bence Jones proteinuria, albumin/globulin reversal in all 48 (100%). These findings are consistent with previously published studies (3-5,11-14).

There are multiple reports of MM with RPPF presentation (11,15,16). Similarly in our study we had four patients of MM with RPRF who were diagnosed to be light chain myeloma on serum FLC assays.

In our study with a median follow-up of 9 weeks, 30 patients (62.5%) had complete renal response and 8 patients (16.6%) were dialysis dependent. Bladé et al (13) in their study on 94 MM patients with renal failure reported serum creatinine level (<4 mg/dL), serum calcium level (≥11.5 mg/dL) and amount of proteinuria (<1 g/24 h) were associated with renal function recovery. Similarly we found higher serum creatinine, presence of oliguria, RRT requirement and AKI stage III associated with poor renal recovery. However urine protein (g/day) was similar between patients with and without renal recovery. Probably because of more number of oliguric patients in poor renal recovery group could have underestimated the 24 hours urine protein quantification.

In our study hypercalcemia was the common precipitating factor for AKI. Patients with hypercalcemia had better renal recovery in comparison with normal serum calcium.

Rana et al (17) in their UK NCRI myeloma XI trial to determine renal outcome in patients with newly diagnosed MM involving 2334 patients (patients requiring RRT were excluded) reported age <70 years, male gender, baseline

![Figure 2. Distribution of stage of AKI in the study population.](image)

![Figure 3. Distribution of type of myeloma in the study population.](image)

![Figure 4. Renal outcome with time period in the study population.](image)
serum FLC level >1000 mg/L and/or a FLC response of ≥90% associated with improved renal function. In comparison with this study we have included patients requiring RRT and could not measure serum FLC levels at follow-up. Yadav et al (18) in their multicentre study on relationship between renal function and serum FLC levels in MM, reported strong relationship between higher serum FLC levels at diagnosis and the severity of renal impairment. Yadav et al (19) in their multicentre study on serum FLC at diagnosis in MCN, reported serum FLC level at diagnosis was neither associated with renal function recovery nor with overall survival. Similarly in our study there was no difference in baseline serum FLC levels and kappa: lambda in patients with and without renal recovery.

Renal failure is common presentation in light chain myeloma (20). There is scarcity of data on light chain myeloma in Indian population. Singh et al (21) reported Indian light chain myeloma patients have significantly different clinico-hematological profile from published studies and found no difference in proclivity to renal failure on comparing with other types of myeloma (IgG or IgA). Conversely in our study presence of light chain myeloma was associated with poor renal recovery. With small sample size and rarity of light chain myeloma it is hard to interpret this association.

Strength of our study is to determine renal outcome in newly diagnosed myeloma patients with AKI, since overall survival of MM depends on renal recovery.

**Conclusion**

In our study in patients with newly diagnosed MM presenting with AKI renal recovery is 62.5%. Factors associated with poor renal recovery are higher serum creatinine, oliguria, RRT requirement, AKI stage III and light chain myeloma. However, in the near future more studies are needed to validate.

**Limitations of the study**

Our study has following limitations: it is a single center study with small population and shorter duration of follow-up. Renal biopsy was not conducted in all patients hence we could not comment on histopathological factors determining renal outcome. Fluorescent in-situ
hybridization was not done for chromosomal anomalies. Less emphasis on extra-renal myeloma features and could not assess serum FLC level for follow-up.

**Authors’ contribution**

SS and HCS were the principal investigators of the study. Both authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. Both authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

The research followed the tenets of the Declaration of Helsinki. The ethical committee of Institute of Medical Sciences; BHU was approved the study (ethical code # ECR /526 /Inst /UP/ 2014 /RR-20/2258). The informed consent was taken from the patients. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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