



## Kidney Injury in Multiple Myeloma: Predisposing Factors, Manifestations & Outcome, Single-centre Experience

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**Abstract:** Introduction: Multiple Myeloma (MM) is third most common hematological malignancy. Renal impairment is observed in 25-75% patients with MM, could be due to disease itself or other unrelated causes, also its second most common cause of death after infection in MM patients. Purpose of this study is to compare clinical & lab parameters of multiple myeloma patients with & without kidney injury also to determine outcome of kidney injury. Results: Between 2017 to 2024, thirty-two patients were diagnosed with MM, their mean age was  $61.62 \pm 12.05$  years, and 78.12% were male. Hypertension (n=11, 34.37%) & diabetes mellitus (n=7, 21.87%) were most common co morbid, and body aches/weakness (62.50%), fractures (17.64%) & anemia (17.64%) were common manifestations. Anemia, hypocalcemia, hypercalcemia & hypoalbuminemia was observed in 56.25%, 21.87%, 25% & 46.87% patients respectively. Kidney injury (KI) (Acute kidney injury or acute on chronic kidney disease) was observed in 68.75% patients, and mortality was 43.75%. MM patients with kidney injury (MM-KI) belonged to older age ( $63.77 \pm 11.15$ ) group than MM patients with normal kidney functions (MM-NKF) ( $59.5 \pm 14.5$ ) ( $p=0.255$ ), their mean creatinine was  $1.8(1.65)$  mg/dl, & proteinuria was  $255.5(450.25)$  mg/day. Nine patients (40.90%) require renal replacement therapy in form of hemodialysis during course of treatment, and 18(81.81%) patients had full or partial recovery of renal functions. Mean hemoglobin & albumin was statistically significantly low in MM-KI group than MM-NKF, however fracture & anemia was more frequent among MM-NKF group, but statistically insignificant. Overall one, three & five-year survival rate for MM patients was 97%, 81% & 62% respectively. Conclusion: Our study showed that higher mortality was observed in MM patients with kidney injury. Early intervention of kidney injury predisposing factors may affect the renal & mortality outcome. This is one of few reported data on MM patients in UAE, we hope that further studies involving multicentric approach in MM patients could provide more detailed overview of kidney disease in these patients.

Multiple myeloma (MM) is defined by deleterious proliferation of monoclonal plasma cells, that destroy microenvironment of bone marrow and result in overproduction of monoclonal immunoglobulins (Ig), immunodeficiency & osteoclast hyper-activation (1-3). Myeloma is third most common hematological malignancy with global incidence of 1.96 cases per 100,000 population in 2019 (4), while reported incidence in Dubai is 2.9-4.7/100,000 populations between 2014 to 2023 (5). It is more common in men & elderly individual with median diagnosis age of 65 years, while less than 3% of patients present at  $\leq 40$  years of age (6-8). Obesity, ionizing radiation, chronic antigen stimulation, genetics, environmental

exposure like certain occupations i.e. farming & agriculture are potential risk factors (9-12). Genetic mutations like t (4;14), t (14;16), t (14;20), deletion 17p , gain 1q, or p53 mutation is associated with development of high-risk multiple myeloma (13). Pathogenesis of MM involves initial formation of precursor plasma cell clones, and its transformation into malignant plasma cell myeloma (9,14.). MM is suspected when serum electrophoresis yield paraprotein more than 30 g/l and confirmed by more than 10% plasmacytosis in bone marrow biopsy (14), anemia, recurrent infection, renal impairment, osteolytic bone lesions & hypercalcemia are common presentations (1,2 9). Renal impairment is observed in 25-75% patients with MM, could be due to disease itself or other unrelated causes, also its second most common cause of death after infection in MM patients (15). MM is quite difficult to suspect in pre-existing kidney disease patients as usual clinical symptoms & signs aid in diagnosis of MM are not useful in presence of CKD. CKD patients may present with acute deterioration of renal functions, resistant anemia and pathological fractures. Purpose of this study is to compare clinical & lab parameters of multiple myeloma patients with & without kidney injury also to determine outcome of kidney injury.

### **PATIENTS & METHODS**

This retrospective study was carried out in Dubai hospital, Dubai. It includes 32 MM patients who were followed up in span of 7 years (2017 to 2024). Patients with suspected MM were evaluated with detail history focusing on body aches/weakness, fractures & anemia. Laboratory work up includes blood count, renal functions, serum calcium, albumin, free light chain, urine studies for proteinuria & histopathology diagnosis using tissue biopsy. Qualitative data were displayed in cross tabulations, and quantitative data were described in terms of arithmetic mean  $\pm$  standard deviation. Bivariate techniques were used for initial evaluation of contrasts. Thus, Chi-square and Fisher's exact tests were used for comparisons of frequencies of qualitative variables; Mann-Whitney test and the unpaired t-test were used for comparisons of means of two quantitative variables.  $P < 0.05$  was considered statistically significant. Graft and patient survival rates were assessed using Kaplan-Meier method. All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

### **RESULTS**

Between Year 2017-2024 34 patients were diagnosed with Multiple myeloma, two of them were known case of Chronic kidneys disease on maintenance hemodialysis so were excluded. Their mean age was  $61.62 \pm 12.05$  years, 65.62% (n=21) were above 60 years of age also male (n=25, 78.12%) were predominant gender in our study group. Hypertension (n=11, 34.37%) & diabetes mellitus (n=7, 21.87%) were most common co morbid, and body aches/weakness, fractures & anemia were common manifestations seen in 20(62.50%), 6(17.64%), 6(17.64%) patients respectively. 62.50% (n=20) patients were suffering from Kappa predominant light chain MM, while 12(37.50%) patients had lambda variant of MM. Laboratory parameters analysis showed median (IQR) hemoglobin was 9.25(3.2) g/dl, serum calcium (corrected) was 9.3(1.4) mg/dl, serum albumin was 3.65(1.05) g/dl & serum creatinine was 1.4(1.63) mg/dl whereas anemia, hypocalcemia, hypercalcemia & hypoalbuminemia was observed in 18(56.25%),7(21.87%),8(25) & 15(46.87%) patients respectively. Kidney injury(KI) (Acute

kidney injury or acute on chronic kidney disease) was observed in 68.75%(n=22) patients, and mortality was 43.75% (n=14) among MM patients during study period. The mean age(years) was  $63.77 \pm 11.15$  &  $59.5 \pm 14.5$  ( $p=0.255$ ) for MM patients with kidney injury (MM-KI) & with normal renal functions (MM-NKF) respectively, 77.27%(n=17) of MM-KI patients were above 60 years of age while 50% of MM-NKF patients belonged to 40-60 years of age, however male gender was predominant in both groups [MM-KI vs MM-NKF: 86.36%(n=19) vs 60% (n=6),  $p=0.094$ ]. Regarding manifestations, fractures incidence [MM-KI vs MM-NKF: 13.63%(n=3) vs 30% (n=3),  $p=0.271$ ] & anemia [MM-KI vs MM-NKF: 13.63%(n=3) vs 30% (n=3),  $p=0.271$ ] was more common in MM-NKF, while body aches & weakness was more common in MM-KI group [MM-KI vs MM-NKF: 63.63%(n=14) vs 60% (n=6),  $p=0.290$ ]. Kappa light chain dominant MM was more common in both groups. In MM with kidney injury patients, Median (IQR) hemoglobin & serum albumin levels were comparatively low i.e.  $9.15(2.16)$  g/dl &  $3.55(1.2)$  g/dl ( $p > 0.05$ ) respectively also 63.63% (n=14) & 50% (n=11) patients had anemia and hypoalbuminemia respectively, whereas median (IQR) corrected serum calcium level was better in myeloma patients with kidney injury than normal renal functions patients [MM-KI vs MM-NKF:  $9.3(1.4)$  vs  $9.2(0.95)$ ,  $p=0.762$ ], however hypocalcemia & hypercalcemia frequency was more in kidney injury patients i.e. 5(22.72%) & 6(27.27%) patients respectively. The median serum creatinine in Kidney injury patients were  $1.8(1.65)$  mg/dl, & proteinuria was  $255.5(450.25)$  mg/day, only three patients (13.63%) had more than 2 gm proteinuria per day, while fifteen patients (68.18%) had proteinuria less than 300 mg/day. Nine patients (40.90%) require renal replacement therapy in form of hemodialysis during course of treatment, and 18(81.81%) patients had full or partial recovery of renal functions. Overall one, three & five-year survival rate for MM patients was 97%, 81% & 62% respectively.

Patient characteristics	All myeloma Patients (n=32)	Myeloma Patients with normal renal functions(n=10, 31.25%)	Myeloma patients with Kidney injury (n=22, 68.75%)	p-value
Age in Years, Mean $\pm$ SD	61.62 $\pm$ 12.05	59.5 $\pm$ 14.5	63.77 $\pm$ 11.15	0.255091
<40 years	2(6.25)	1(10)	1(4.54)	
40-60 years	9(28.125)	5(50)	4(18.18)	
> 60 years	21(65.62)	4(40)	17(77.27)	
Gender				
Male n(%)	25(78.12)	6(60)	19(86.36)	0.094497
Co-morbid				
Hypertension	11(34.37)	3(30)	8(36.36)	0.725359
Diabetes Mellitus	7(21.87)	1(10)	6(27.27)	0.27328
Congestive Heart failure	3(9.37)	1(10)	2(9.09)	0.934824
Benign Prostate Hyperplasia	3(9.37)	0(0.00)	3(13.63)	0.219949
Chronic Kidney disease	2(6.25)	0(0.00)	2(9.09)	0.324756
Atrial Fibrillation	1(3.12)	0(0.00)	1(4.54)	0.493352
Hyperthyroidism	1(3.12)	0(0.00)	1(4.54)	0.493352
Hypothyroidism	1(3.12)	1(10)	0(0.00)	0.131818
Osteoporosis	1(3.12)	0(0.00)	1(4.54)	0.493352
Manifestations				
Body aches & weakness	20(62.50)	6(60)	14(63.63)	0.290466
Fracture	6(17.64)	3(30)	3(13.63)	0.271651
Anemia	6(17.64)	3(30)	3(13.63)	0.271651

Neuropathy	1(3.12)	0(0.00)	1(4.54)	0.493352
Myeloma type				
Kappa	20(62.50)	8(80)	12(54.54)	0.16801
Lambda	12(37.50)	2(20)	10(45.45)	0.16801
Kidney Injury	22(68.75)			
Renal replacement therapy	9		9(40.90)	
Lab parameters				
Hemoglobin g/dl, Median (IQR)	9.25(3.2)	11.35(3.02)	9.15(2.16)	0.428115
<10 g/dl, n%	18(56.25)	4(40)	14(63.63)	
Calcium mg/dl, Median (IQR)	9.3(1.4)	9.2(0.95)	9.3(1.4)	0.762525
<8.5 mg/dl	7(21.87)	2(20)	5(22.72)	
8.5-10.2 mg/dl	17(53.12)	6(60)	11(50)	
>10.2 mg/dl	8(25)	2(20)	6(27.27)	
Albumin g/dl, Median (IQR)	3.65(1.05)	3.65(0.72)	3.55(1.2)	0.79299
<3.5 g/dl	15(46.87)	4(40)	11(50)	
Creatinine mg/dl, Median (IQR)	1.4(1.63)	0.75(0.17)	1.8(1.65)	0.001523
> 1.2 mg/dl	22(68.75)	0(0.00)	22(100)	
Urine routine				
Hematuria	2(6.25)			
Proteinuria mg/day, median (IQR)	668.25(568.25)		255.5(450.25)	0.706109
< 300 mg	25(78.12)	10	15(68.18)	
300 mg to 2gm	4(12.5)	0	4(18.18)	
> 2 gm	3(9.37)	0	3(13.63)	
Mortality	14(43.75)	0(0.00)	14(63.63)	

## DISCUSSION

Renal complications are frequent in MM, because half of the patients may experience renal insufficiency (acute or Acute on chronic) during course of the disease (16). The prevalence of AKI in literature varies with reference creatinine; 30%, 20% & 15% using serum creatinine 1.5, 2 & 2.3 mg/dl respectively (17 -18.). In our study population, Kidney injury was reported in 68.75% MM patients using creatinine 1.5 mg/dl cut off. Estimated glomerular filtration rate (eGFR) is used for KI diagnosis according to International myeloma working group criteria (<40 ml/min) however its use is being criticized as it is appropriate for chronic kidney disease staging (19.), however its difficult to assess AKI in absence of baseline creatinine. RIFLE (Risk, Injury, failure, Loss of kidney function & End stage kidney disease) was used as criteria of KI diagnosis by Shi et al, and reported AKI incidence of 35%. To diagnose light chain cast nephropathy (LCCN), require renal biopsy, also true incidence of LCCN is not known. Ecotiere et al did renal biopsy of 72 out of 127 patients for severe renal injury or significant albuminuria, pure LCCN was diagnosed in 41, other four had co-existing other nephropathies. 25% had other light chain (LC) induced renal disease including AL amyloidosis (n=12), LC deposit disease (n=6) & Fanconi syndrome (n=1) (20). The cause of Kidney injury in MM may & may not be related to monoclonal immunoglobulin(MIg) related. Hypocalcemia, dehydration, infection, NSAIDs & bisphosphonates are non MIg related causes

of Kidney injury. We observed hypercalcemia is in 25% patients of MM & 27.27% patients of MM with KI in our study population. Bilmark et al reported hypercalcemia in 15% of MM patients (21), also it is observed that higher prevalence of hypercalcemia (25-45%) with elevated serum creatinine (22). Hypercalcemia is considered important for diagnosis of MM, however CKD patients commonly use calcium & vitamin D analogues so only persistent hypercalcemia despite stopping these medicines may indicate toward myeloma. Anemia is common complication of MM, occurring in 80% of patients (23), result from multiple pathophysiological mechanism like abnormal myeloma cells replacing medullary progenitor cells, cytokine (TNF alpha, IL1, IL6 & CCL3) suppress erythropoiesis, abnormal iron metabolism & anemia of chronic disease (24-26.). In renal impairment, relative erythropoietin deficiency, decrease red bell cell life span also leads to anemia. Anemia in MM predispose to kidney injury. Anemia is an important clue for MM diagnosis however as it occurs in both MM & renal impairments so not quite useful in that setting. It is difficult to assess whether anemia is only a consequence of MM or causing hypoxia that may lead to progression of CKD or establishment of AKI (25,26).

We have observed incidence of anemia in MM is 18.75%, and 13.63% in MM with KI. Both anemia & hypercalcemia were not significantly associated with Kidney injury in our study population, however Cesar B.N et al found anemia in 57.48% & 54% in MM patients & MM with KI patients respectively and it was significantly associated with Kidney injury, while hypercalcemia was observed in 18.56% & 74% MM & MM with KI patients respectively however this correlation was not statistically significant (27). Proteinuria is a potential risk factor for renal impairment in MM patients. in our study population, significant proteinuria (> 300 mg/day) was observed in 31.81% MM-KI patients. Proteinuria in MM occur for number of reasons; excessive production, filtration & excretion of monoclonal component, increase glomerular permeability & tubular proteinuria due to proximal tubular cell injury. Paraproteins mainly free light chains affect kidneys in number of ways; formation of cast (cast nephropathy), direct damage to tubular cells (Fanconi syndrome/acute tubular necrosis), inflammatory pathway activation (acute & chronic Glomerulonephritis & tubulointerstitial nephritis) & deposit disease caused by intact or modified monoclonal proteins (Amyloidosis) (28) Cesar BN et al found proteinuria > 1gm per day significant factor for renal impairment in MM patients (27), also Knudsen LM suggest higher level of proteinuria is associated with renal impairment irrespective of its origin. (18). In our study population, 45% (n=20) had normal renal functions at the time of diagnosis, mortality rate was higher among kidney injury patients. Cesar et al found baseline GFR > 60 ml/min/1.73m<sup>2</sup> is associated with better renal response (27), as greater renal reserves determine greater chance of renal recovery. Interventions to deal with predisposing factors for kidney injury like hydration, withdrawal of nephrotoxins & treatment of hypercalcemia should be started immediately, also rapid & early reduction of monoclonal concentration is necessary to achieve renal response & great survival. A UK study on 3107 MM patients between 1980 to 2002 reveal early mortality associated with renal dysfunction (29), also Chinese study showed that MM patients with glomerular filtration rate < 30 ml/min and lack of renal response is associated with shorter survival (30) and Courant et al found best renal response in MM patients associated with best hematological response in absence of chronic kidney disease (31). Main limitation of our study is observational retrospective type of study & small sample size, also treatment and MM response was not available to comment.

## CONCLUSION

Our study showed that higher mortality was observed in MM patients with kidney injury. Early intervention of kidney injury predisposing factors may affect the renal & mortality outcome. This is one of few reported data on MM patients in UAE, we hope that further studies involving multicentric approach in MM patients could provide more detailed overview of kidney disease in these patients.

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