Influence of Renal Impairment on Outcome of Patients with Multiple Myeloma: A Ten-year Single Center Experience

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ABSTRACT

Background: *Renal impairment is an important complication occurring in 20-50% of newly diagnosed patients with multiple myeloma. It adversely affects overall survival and outcome in these patients. This study aims to assess RI in newly diagnosed multiple myeloma patients presenting at a tertiary hospital in the South-South region of Nigeria.*

Methods: *This was a ten-year retrospective study conducted on cases with confirmed multiple myeloma from August 2006 to July 2016. Renal impairment was determined using eGFR formula calculated by MDRD formula. Data analysis was done using statistical software package Microsoft Xcel® 2013.*

Results: *A total of 29 patients were diagnosed with MM within the period, with a male to female ratio of 1.9: 1. The median age at diagnosis was 60 years. Renal impairment occurred in 15 (51.7%) of cases. One (6.7%) patient presented with eGFR <15 signifying end stage renal disease requiring dialysis. Significantly more patients with lambda chain disease had RI compared to patients with kappa chain disease. Patients with RI were significantly more at risk of death than those with normal renal function [hazards ratio 12.1 at 95% CI; p = 0.03]. The group with RI had an estimated 5-year OS of 40.8% compared to those without RI who had an OS of 85.7%; (hazards ratio 2.46, at 95% CI).*

Conclusion: *Renal impairment remains a common presentation in patients newly diagnosed with multiple myeloma. The presence of RI at diagnosis is a poor prognostic feature affecting survival of myeloma cases.*

Key words:

INTRODUCTION

Multiple Myeloma (MM) is characterized by the neoplastic proliferation of clonal plasma cells associated with production of paraproteins and causing end organ damage which manifests as hypercalcaemia, renal impairment (serum creatinine>177 µmol/L or 2.0 mg/dL), anaemia and lytic bone lesions. The median age at diagnosis is 65 – 71 years in the western world with most cases occurring at age >60 years, however Africans have reported a lower age of presentation incidence.[1] The disease affects people of African descent more than Caucasians and has a male preponderance.

Depending on the criteria used, renal impairment is seen in 20-50% cases of

myeloma at diagnosis, therefore making it a common presentation. About 30% - 50% of the newly diagnosed MM patients have a serum creatinine above 115 µmol/L (or 1.3mgl/L), while severe renal insufficiency with serum creatinine >177 µmol/L (or 2.0 mg/dL) occurs in 15% - 20% of cases and about 10% of cases require prompt dialysis.[7] However kidney function is best assessed by the estimated glomerular filtration rate (eGFR) because the creatinine values vary according to age, sex and muscle mass- which is usually reduced in the elderly. Since serum creatinine may underestimate the degree of renal insufficiency, the eGFR calculated using the Modification of Diet in Renal Disease (MDRD) formula and classified based on Kidney Disease Improving Global Outcomes classification have been recommended for the assessment of RI in MM patients by the International Myeloma Working Group.[7]

There are several pathogenic mechanisms behind the development of renal impairment in MM, the most common being myeloma cast nephropathy (90% cases) which arises as a result of the toxic effects of free light chain deposited primarily in the renal tubules, leading to intra-tubular cast formation, atrophy and obstruction. The pathogenesis of RI in MM less frequently may also be due to monoclonal immunoglobulin deposition disease involving the glomeruli, amyloidosis, direct infiltration of the kidney by plasma cells, acquired Fanconi's syndrome, or renal tubular acidosis. Hypercalcaemia, volume depletion, recurrent urinary tract infections, use of non-steroidal anti-inflammatory drugs and contrast media have also been implicated, amongst others. Renal impairment in MM is one of the complications that requires careful attention as it predicts survival.[7,,,]

AIM AND METHODS

This study aims to assess renal impairment in newly diagnosed multiple myeloma patients presenting at a tertiary hospital in South-South region of Nigeria. This was a hospital-based retrospective study conducted at the University of Port Harcourt Teaching Hospital which is a tertiary institution in the South-South region of Nigeria. Data was obtained from the case notes retreived from both the department of haematology and blood transfusion, medical wards and the medical records department. All confirmed cases of MM between August 2006 and July 2016 were included in the study. Diagnosis of MM was made using bone marrow aspiration, presence of monoclonal protein on serum protein electrophoresis and/ or serum free light chains analysis. Biodata extracted included age, sex and ethnicity. Other data included laboratory investigations done at first presentation: haemoglobin concentration, erythrocyte sedimentation rate (ESR), serum electrolytes, urea and creatinine (EUCR), serum protein electrophoresis (SPE) and serum free light chains (FLC). Renal impairment was determined using eGFR calculated by the MDRD formula. Data was analyzed using statistical software package Microsoft Xcel® 2013. Results were expressed in means [±SD] for continuous variables and percentages for categorical variables as well as using tables and figures. P-values <0.05 were taken as statistically significant. Cox regression analysis was used to assess survival rate.

RESULTS

A total of 29 patients were diagnosed with

MM within the period, out of which 19 (65.5%) were males and 10 (34.5%) were females, giving a male to female ratio of 1.9: 1. The median age at diagnosis was 60 years with a mean age of 54.2 ± 15.9 years. *Table 1* gives the mean haemoglobin concentration, erythrocyte sedimentation rate (ESR) and biochemical parameters assessed for the total population of myeloma cases at diagnosis. Renal impairment was seen in 15 (51.7%) of the cases. Majority (n=22, 75.9%) of the patients had anaemia at presentation with haemoglobin concentration<10g/dL. More patients with RI had anaemia (80%) compared to the patients without RI (63.6%), but this was not statistically significant, p= 0.09. The mean haemoglobin of the total myeloma population was 8.4g/dL, but the mean Hb. conc. of patients with RI was statistically significantly lower (7.8g/dl) compared to those without RI (9.3g/dL), p=0.047. The mean ESR was markedly elevated at 107.5mm/Hr, with the ESR of those with RI significantly higher (130.5mm/Hr) than MM cases without RI (78.6mm/Hr), p=0.009.

The sodium, potassium and bicarbonate values were comparable between patients with and without RI, but the urea and creatinine were higher in the group with RI, they also had lower eGFR, see *Table 1*. Eight (27.6%) patients had elevated serum creatinine levels >115µmol/L, however 15 patients (51.7%) had renal impairment (RI) based on estimated glomerular filtration rate (eGFR) values of <90 at the time of diagnosis of MM, while 14 (48.3%) did not have RI.

Figure 1 shows the stages of renal disease in those with RI. In the group with RI, 8 (53.3%) patients had elevated creatinine levels above normal reference values, there were 7 (46.7%) cases with normal serum creatinine but had RI based on eGFR values for determining RI. Using the CRAB criteria[1], there were 3 (10.3%) cases that had severe RI based on serum creatinine values >177µmol/L while 4 (13.8%) had eGFR values <40ml/min. Only one patient (3.4%) of the total population and 6.7% of the RI group presented with eGFR <15 signifying end stage renal disease (ESRD) and requiring dialysis.

Other biochemical parameters including the uric acid, total proteins, albumin and adjusted calcium were not significantly different between both groups. Only one patient (3.4%) had hypercalcaemia, however the patient had renal impairment. All of the myeloma cases who had Bence Jones protein analysis done had positive results regardless of renal status. Majority (89.7%) of the patients had paraprotein secretion while 3 cases (10.3%) did not secrete paraproteins. These 3 cases had grossly abnormal free light chain assay and ratio that were diagnostic [they all had kappa chain involvement with values of 1065, 890 and 5850 mg/L respectively with normal lambda chain values]. The mean paraprotein concentration was similar in both groups with and without RI. Free light chain assay was done for 13 (44.8%) of the cases, none of these had normal values. Of these, 5 (38.5%) had kappa chain involvement with mean kappa chain value of 1916.2 g/L, *range 310 – 5850 g/L*; four (30.8%) had lambda chain involvement with mean lambda chain value of 4124.4 g/L, *range 156 – 12352 g/L*; while 4 had kappa chains elevated above normal but <100g/L, mean 60.5 g/L, range 28.4 – 73.5 g/L. More patients with lambda chain disease (66.7%)

had RI compared to those with kappa chain disease (44.4%), p=0.002.

With regards to survival, the median follow-up was 22.8 months [range 2 – 84 months] for the myeloma patients, with an estimated five-year overall survival (OS) rate of 49.5%. Using Cox regression analysis, patients with RI were significantly more at risk of death than those with normal renal function [hazards ratio 12.1 at 95% CI; p = 0.03]. Figure 2 shows the Kaplan-Meier plot of estimated survival for the two groups of myeloma cases. The myeloma group with RI had an estimated 5-year of 40.8% with twice as much deaths compared to those without RI who had an estimated 5-year OS of 85.7%; (hazards ratio 2.46, at 95% CI).

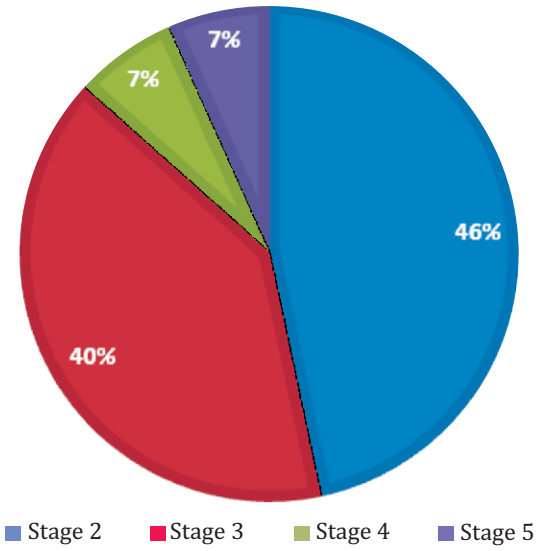

Figure 1: Stages of Chronic Kidney Disease seen in Myeloma Cases with Renal Impairment

Stage 1- GFR > 90 mL/min; *Stage 2* Mild CKD - GFR = 60-89 mL/min; *Stage 3*- Moderate CKD - GFR = 30-59 mL/min; *Stage 4*- Severe CKD- GFR = 15-29 mL/min; *Stage 5*- End Stage CKD - GFR <15 mL/min[13]

Table 1: Comparison of Variables between groups with and without renal impairment

Parameter	Total Myeloma cases (n=29)		Myeloma With Renal Impairment (n=15)		Myeloma Without Renal Impairment (n=14)		P-value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	54.2	15.9	55.4	15.7	52.4	14.1	0.602
Weight (Kg)	75.9	15.6	75.4	18.1	76.8	10.5	0.85
Hb. conc. (g/dL)	8.4	1.8	7.8	1.7	9.3	1.8	0.047*
ESR (mm/Hr)	107.5	45	130.5	28.6	78.6	47.8	0.009*
Sodium (mmol/L)	137.4	6.4	139.1	5.0	135.2	7.5	0.15
Potassium (mmol/L)	4	0.8	4.1	1.0	4.9	0.7	0.54
Bicarbonate (mmol/L)	22.2	14.7	21.6	4.4	29.2	21.3	0.27
Urea (mmol/L)	4.6	2.6	6	2.3	2.7	1.6	0.0003*
Creatinine (µmol/L)	122.8	92.4	162	105.7	69.4	16.4	0.005*
eGFR (ml/min/1.73m^2)	70.4	23.9	55.9	22.3	90	0	<0.0001*
Uric Acid (µmol/L)	476.7	237.6	505.5	253.1	429.9	217.9	0.48
Corrected Calcium (mmol/)	2.3	0.3	2.4	0.2	2.2	0.3	0.35
Total Protein (g/L)	93	35.3	100.2	32.8	87	40.4	0.468
Albumin (g/L)	29.9	7.3	31.1	10.0	32.4	10.2	0.79
Paraprotein concentration (g/L)	37.9	36.8	47.9	38.8	27.6	39.2	0.28
Kappa chains (mg/L)	791	1593	1044.3	2357.2	595.6	625.7	0.67
Lambda chains (mg/L)	1278	3476.4	2095.4	5025.0	78.9	168.0	0.37

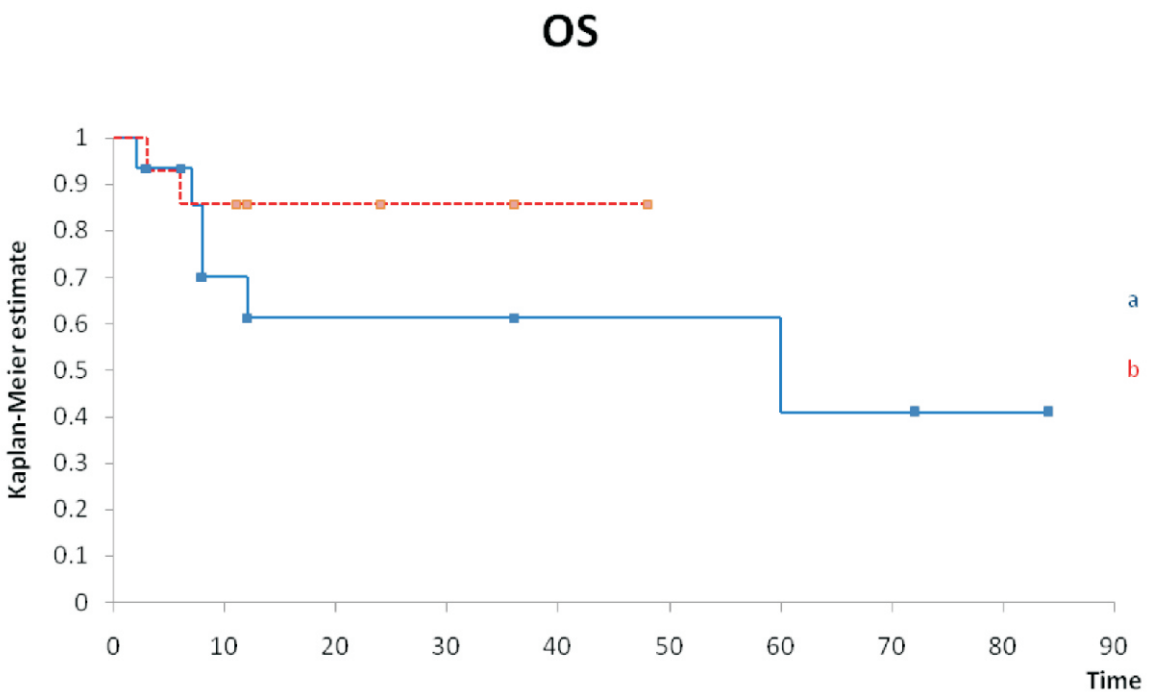

Figure 2: Kaplan-Meier Plot of Estiated Survival in Myeloma Patients with and without Renal Impairment.

OS- overall survival; "a" refers to myeloma patients with renal impairment; "b" refers to myeloma patients without renal impairment.

DISCUSSION

Renal impairment remains an important complication and presenting feature in multiple myeloma. More than half of our cases presented with renal impairment with a majority in CKD stages 2 and 3. Although RI in MM has been reported to occur in 20 – 50%, a Tunisian study of 144 patients reported a remarkably higher prevalence of 90.9% cases with RI at diagnosis. Despite the high incidence of RI in our patients, severe RI with eGFR <30ml/min was seen in only 6.9%, this is lower than quoted for other studies which show that about 10% of cases have severe RI at presentation.[7] Our study also showed a lower incidence of ESRD (3.4%) compared to other studies (4 – 10%).[7] Presence of ESRD correlates with a high tumour burden and impacts negatively on outcome of the patients.[8,15] The small number of cases we studied may have accounted for this low number. Our study supports the fact that using serum creatinine values alone does not truly reflect renal function as a little over a quarter had elevated serum creatinine values, but when using eGFR to determine RI this number increased with more than half of the cases having RI, making eGFR more accurate in assessing renal function. The eGFR was calculated using the MDRD formula as recommended by the

International Myeloma Working Group although the staging of kidney disease based on eGFR values applies to chronic kidney disease. However, kidney diseases in myeloma may present as acute kidney injury, nephrotic syndrome or chronic kidney disease or Fanconi's syndrome. Acute kidney injury may progress to chronic kidney disease.[15]

This study did not investigate the causes of the renal impairment in these patients and none of them had renal biopsy and histology. However, the patients with RI had higher mean free light chains (FLC) concentration compared to patients without RI. Light chain cast nephropathy may have accounted for the renal impairment in the majority of our cases, because cast nephropathy is the commonest cause of RI in MM. Myeloma which produces only free light chains accounts for 40 – 60% of severe renal failure, signifying the toxic effects of the free light chains.[10] Of the free light chains, lambda chains are more nephrotoxic than kappa chains as seen in our study where significantly more patients with lambda chain disease had RI compared to those with kappa chain disease. Kappa chains tend to cause nephrotoxicity at much more higher concentrations than lambda. Although not all the patients had FLC assay done as this was not available in the earlier years of analysis, the ESR was significantly higher in patients with RI and this may support that cast nephropathy may have played a major role in the patients with RI. Therefore, although the FLC was higher in RI patients, it was not statistically significantly and this may be have been due to the small number of cases who had FLC done. The ESR is an old test that was used for screening for MM, but it still plays an important role in the diagnosis and monitoring of myeloma in our environment, for patients who may not be able to afford serum protein electrophoresis (SPE) and FLC analysis, moreover these tests are not yet readily available in our environment. Plasma exchange and high cut-off dialysis have been used to remove the toxic light chains, thereby improving renal function. These procedures unfortunately were not available in our centre, therefore no patient benefitted from it. Hypercalcaemia did not seem to play a major role in the development of RI in our patients because only one patient had hypercalcaemia. There was no patient with amyloidosis.

Anaemia is present in about 60- 80% of myeloma cases at diagnosis, and this was a similar finding in our study where 75.9% of our patients had anaemia. There were more people with RI who had anemia but there was no significant difference in the prevalence of anaemia between those who had RI or not. However, the mean haemoglobin concentration was significantly lower in the group with RI compared to those without RI. The kidneys is responsible for the production of more than 90% of erythropoietin which is a growth factor necessary for erythropoiesis. In patients with RI, there is reduced synthesis of erythropoietin and its deficiency plays a major role in the development of anemia of CKD. However, the cause of anaemia in MM is multi-factorial and other factors such as production of cytokines which induce apoptosis of erythroblasts, upregulation of hepcidin and bone marrow infiltration of plasma cells are all important in the aetiology of anemia in MM.[17,18]

Our study showed that RI affected survival of the myeloma patients, since there were twice as much deaths in the group with RI than those without RI. This confirms findings from other reports which state that the presence of RI is a poor prognostic feature which affects outcome of newly diagnosed myeloma patients. [7, 8, 9, 15, 17] Therefore immediate identification of patients with RI and prompt intervention goes a long way in affecting the overall survival and outcome of these patients.

CONCLUSION

Renal impairment remains a common presentation in patients newly diagnosed with multiple myeloma. More than half of our patients presented with RI. Patients with RI had significantly lower haemoglobin concentration, higher serum urea and creatinine concentrations and also had higher concentrations of free light chains. Significantly more patients with lambda chain disease had RI compared to patients with kappa chain disease. Mortality in the patients with RI was twice as much than in those without RI, making the presence of RI at diagnosis a poor prognostic feature affecting survival of myeloma cases.

CONFLICT OF INTEREST: None to declare.

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