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Association of Myeloma in Patients of Chronic Kidney Disease; A Single Centered Study

Farzana Adnan Sheikh, Syed Tajammul Ali, Sidra Rashid, Mehwish Qamar, Khadijah Abid

ABSTRACT

Objective: To evaluate the frequency along with socio-demographic factors and clinical features of myeloma in patients with chronic kidney disease (CKD) presenting at a tertiary care hospital in Karachi, Pakistan.

Study design and setting: It was a cross-sectional study conducted at the Department of Nephrology and Hematology, Liaquat National Hospital, Karachi, Pakistan from Jan 2022 to Jul 2022.

Methodology: Patients of age>18 years of either gender having chronic kidney disease were included in the study. Detailed data regarding socio-demographic factors, clinical features and presence of multiple myeloma was obtained. Myeloma was diagnosed in the patients using WHO criteria i.e. presence of M-protein in urine or serum, presence of clonal plasma cells in bone marrow, and related tissue or organ failure. Data was entered and analyzed using SPSS version 25.

Results: The median age of the patients with chronic kidney disease was 54 years and most of them were males (63%). Myeloma was detected in only 14 patients with CKD. The proportion of myeloma was similar across chronic kidney disease stages, and statistically there was no significant association between chronic kidney disease stages and myeloma with p-value=0.08. There were no differences in hemoglobin, serum calcium, serum albumin, serum total protein, albumin/globulin (A/G) ratio, ESR, comorbid in patients with and without myeloma (p>0.05).

Conclusion: The frequency of myeloma among patients with chronic kidney disease was low.

Keywords: Chronic Kidney Disease, End Stage Renal Disease, Myeloma

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INTRODUCTION:

Myeloma is a type of blood cancer characterized by abnormal plasma cells growth in the bone marrow.[1] Due to the fact that 90% of patients have multiple bone lesions at the time of presentation, it is frequently referred to as multiple myeloma.[2] Worldwide, myeloma accounts for 1% of all cancers and is the 2nd most frequent hematological malignancy.[3] Globally, the annual incidence of mylemo is 1.2 per 100,000 individuals and median age at the time of diagnosis is 70 years.[3] Approximately, 20% of myeloma patients have genetic abnormalitites and remaining 80% have chromosomal abnormalities.[4] In Asian population, an expeditious raised in the myeloma incidence is significant cause of great distrubance in the healthcare settings.[5]

Myeloma is more common in people of age more than 64 years, accounting for greater than 60% of incidences and 78% of deaths.[1] Furthermore, according to GLOBOCON 2020, the incidence of myeloma in Pakistan is 1.1% and 1.5% of deaths occurred due to it.[6] In recent years, the prognosis of myeloma has improved, from five year survival rate of 30% in 1990, when high-dose dexamethasone and melphalan were the only treatments to greater than 45% in 2006, with the advent of new agents and to greater than 50% in 2011.[1] Myeloma is found to be associated with various clinical manifestations like anemia, infection, renal impairment and bone, influencing mainly older age group and male gender.[1,3] There are various other environmental and genetic factors that have been suspected in the causes and pathogenesis of multiple myeloma, particularly radiation, pesticides, and chemicals such as asbestos, benzene, and arsenic.[5]

Kidney failure is one of the CRAB criteria i.e. anemia, renal

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failure, hypercalcemia, and bone lesions that shows end organ damage. Kidney failure is one of the most frequent complications of myeloma, and it can influence different parts of kidney consisting the tubules, glomerulus, and interstitium.[4] In multiple myeloma patients, chronic kidney disease occurs mainly as a result of damage caused to renal tubules by FLCs (cast nephropathy). A variety of other nephrotoxic processes may also contribute to this damage including dehydration, hypercalcemia, nephrotoxic drugs, and infection.[7]

At the time of diagnosis, almost 50% of the myeloma cases have significantly decreased kidney function (*estimated glomerular filtration rate* less than 60 mL/minute/1.73m^2), with 10 to 15% needing hemodialysis and approximately 1% progressing to end-stage kidney disease.[8,9] A Pakistani research also shows 35% of the myeloma patients had renal impairment (serum creatinine>2 mg/dl) at the time of diagnosis.[5] Studies by Mok et al. revealed that chronic kidney disease is positively associated with mortality among myeloma patients. Whereas, there was increased incidence of multiple myeloma in patients with reduced *estimated glomerular filtration rate* and dipstick proteinuria, the total multiple myeloma cases were 107 only, limiting conclusion of dose-response association and interactive effects of proteinuria and *estimated glomerular filtration rate*.[10,11] Literature has also revealed that improved survival of myeloma patients is linked with reversibility of renal dysfunction.[1,8,10,12] Treatment of myeloma with kidney disease includes removing aggravating factors of renal impairment, drinking enough water, alkalinizing urine, and preventing hypercalcemia as well as hyperuricemia. Dialysis is suitable for myeloma patients with severe renal function.[1,8,10,12]

Even after the advancement in therapeutic agents and supportive care, still the precise mechanisms for the development of myelomas in patients with kidney disease are incompletely understood. In Pakistan, limited data is available regarding the burden of myeloma in chronic kidney disease patients. Thus, in this study, we have evaluated the frequency and clinical features of myeloma along with socio-demographic factors of patients with chronic kidney disease presenting at a tertiary care hospital in Karachi, Pakistan.

METHODOLOGY:

It was a cross-sectional study conducted at the Department of Nephrology and Hematology, Liaquat National Hospital, Karachi, Pakistan for the duration of six months from Jan 2022 to Jul 2022. Sample size of 162 was estimated using frequency of renal impairment as 35%,[5] confidence limit as 7.4%, and level of significance as 5%. Patients of age>18 years of either gender having chronic kidney disease were included in the study. Chronic kidney disease was deemed as positive when patient had estimated glomerular filtration rate of less than 60 ml/minute/1.73m^2 for three months. Stages of chronic disease were labeled as stage 1: estimated glomerular filtration rate greater than 90ml.min/1.73m^2, stage 2: estimated glomerular filtration rate 60-89ml/min/1.73m^2, stage 3: estimated glomerular filtration rate 30-59ml/min/1.73m^2, stage 4: estimated glomerular filtration rate 15-29ml/min/1.73m^2 and stage 5: estimated glomerular filtration rate less than 15ml/min/1/73m^2 (or dialysis). Patients having hemoglobin less than 8 or more than 9 gm/dl, serum calcium level less than 9 mg/dl, anemia sensitive to erythropoietin stimulating agent, and established renal osteodystrophy were excluded from the study. Non-random consecutive sampling technique was applied for sample selection.

Ethical approval from ethical review committee of the Liaquat National Hospital was obtained (ERC# 0743-2022 LNH-ERC). Patients admitted in ward set up and ICU of nephrology department with chronic kidney disease were included. Prior to inclusion, patients were explained the rationale of study and written informed consent was taken from either patients or their families. Detailed data regarding socio-demographic factors (like age, gender), clinical features [like duration of end-stage renal disease (years), duration of hemodialysis, hemoglobin level, serum calcium, serum albumin level, serum total protein, albumin/globulin (A/G) ratio, *erythrocyte sedimentation rate (ESR)*, chronic kidney disease stages, serum immunofixation, serum protein electrophoresis], comorbids (like anemia, hypoalbuminemia, hypercalcemia, diabetes mellitus, hypertension, hyperparathyroidism, vitamin D intoxication] and presence of multiple myeloma was obtained. Myeloma was diagnosed in the patients using WHO criteria i.e. presence of M-protein in urine or serum, presence of clonal plasma cells in bone marrow, and related tissue or organ failure. All details were recorded by a principal investigator on a predesigned proforma having study variables. Exclusion criteria were followed strictly to avoid confounding variables.

Data was entered and analyzed using statistical packages for social sciences (SPSS) version 25. Normality of the numeric data was assessed using Shapiro-Wilk's test. Median and interquartile range were reported for numeric data like age, duration of end-stage renal disease (years), duration of hemodialysis, hemoglobin level, serum calcium, serum albumin level, serum total protein, albumin/globulin ratio, and *erythrocyte sedimentation rate (ESR)*, while frequencies and percentages were reported for categorical data like gender, anemia, hypoalbuminemia, hypercalcemia, anemia, diabetes mellitus, hypertension, hyperparathyroidism, vitamin D intoxication, chronic kidney disease stages, serum immunofixation, serum protein electrophoresis and myeloma. Comparison between chronic kidney disease stages and myeloma was done using Fisher exact test. Comparison between myeloma and socio-demographics, clinical features and comorbids were done using Mann-Whitney U test/Fisher exact test. The p-value less than and equal to 0.05 was considered statistically significant.

RESULTS:

Table 1 shows the baseline characteristics of patients with chronic kidney disease. The median age of the patients with chronic kidney disease was 54 years and most of them were males (63%). At the time of presentation, median hemoglobin was 8.3 g/dl, median serum calcium was 11 meq/l, median serum albumin was 2.6 mg/dl, median serum total protein was 8 mg/dl, median A/G ratio was 0.95 and median ESR was 87, respectively. All patients were anemic, whereas hypoalbuminemia (serum albumin in blood<3.5 gm/dl) was reported in 1.9%, and hypercalcemia (serum calcium>10.7 mg/dl) in 35.8 percent of patients. Almost 35.2% of the patients had stage 4 chronic kidney disease and 33.3% had stage 5 chronic kidney disease. Of 162 patients, 57.4% were diabetic, 42.6% were hypertensive and 22.2% were hyperparathyroidism, respectively.

Out of 162 patients, 51 patients had serum protein electrophoresis tested, of which 12 showed m spike in gamma region. Of 12 patients with M spike in gamma region, 6 had monoclonal and 6 had serum immunofixation. Myeloma was detected in only 14 patients with chronic kidney disease. Figure 1 shows that the proportion of myeloma was similar across chronic kidney disease stages, and statistically, there was no significant association between CKD stages and myeloma with p-value=0.08.

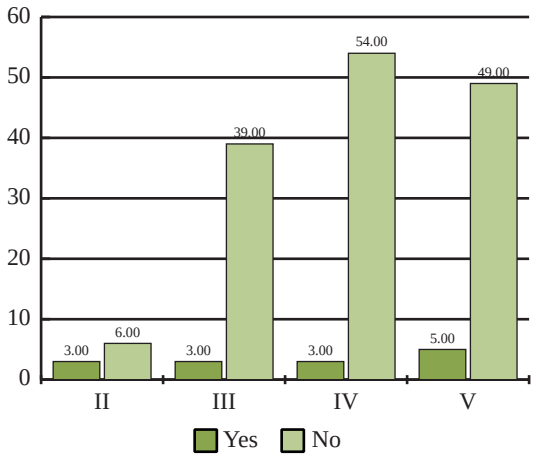
The median age of the chronic kidney disease patients with myeloma was 53.5 years and without myeloma was 54 years. There was no statistically significant relationship between age and myeloma with p-value=0.646. The majority of the patients with myeloma were males (8.8%) and 8.3% were females, however no statistically significant difference was observed between proportions of gender and myeloma with p-value=0.999. The median Hb was 8.45 g/dL of myeloma patients and 8.3 g/dL of without myeloma patients. The difference in Hb level was not statistically significant among patients with myeloma and without myeloma with p-value=0.816. The median serum calcium was 10.8 meq/l of myeloma patients and 11 meq/l of without myeloma patients. The difference in serum Ca level was not statistically significant among patients with myeloma and without myeloma with p-value=0.39. The median serum albumin levels were same for patients with and without myeloma (2.6 mg/dL) with p-value=0.944. The median total protein was same for patients with and without myeloma (8 mg/dL) with p-value=0.599. The median A/G ratio and ESR were also statistically similar between patients with and without myeloma with p-value=0.957 and 0.853. The most frequent comorbid among chronic kidney disease with myeloma was diabetes, followed by hypertension and hyperparathyroidism. There was no statistically significant difference observed in comorbids among patients with and without myeloma (p>0.05). (Table 2)

Table 1: Baseline characteristics of study sample (n=162)

Characteristics	
Age (years)	54 (45-64)
Gender	
Male	102 (63)
Female	60 (37)
Hb level (g/dl)	8.3 (8.0-8.9)
Serum Ca (meq/l)	11 (10.6-13.0)
Serum albumin levels (mg/dl)	2.6 (2.0-3.0)
Serum total protein (mg/dl)	8 (7-8)
A/G ratio	0.95 (0.8-1.0)
ESR	87 (66-100)
Comorbids	
Diabetes	93 (57.4)
Hypertension	69 (42.6)
Hyperparathyroidism	36 (22.2)
Chronic kidney disease stage	
II	9 (5.6)
III	42 (25.9)
IV	57 (35.2)
V	54 (33.3)

Data presented as Median (IQR) or n (%)

Figure 1: Comparison of myeloma and chronic kidney disease stages (n=162)



DISCUSSION:

Myeloma is a type of blood cancer and globally, the annual incidence of myeloma is 1.2 per 100,000 individuals. Due to the fact that 90% of patients have multiple bone lesions at the time of presentation, it is frequently referred to as multiple myeloma.[2] Worldwide, myeloma accounts for 1% of all cancers and is the 2nd most frequent hematological malignancy.[3] According to GLOBOCON 2020, the incidence of myeloma in Pakistan is 1.1% and 1.5% of deaths occurr due to it; kidney failure being one of the most frequent

Table 2: Comparison of socio-demographics, clinical features and comorbids among patients with and without myeloma (n=162)

Characteristics	Yes	No	p-value
Age (years)	53.5 (46-65)	54 (44-62)	0.646
Gender			
Male	9 (8.8)	93 (91.2)	0.999
Female	5 (8.3)	55 (91.7)	
Hb level (g/dl)	8.45 (8-8.5)	8.3 (8-8.9)	0.816
Serum Ca (meq/l)	10.8 (9.9-13)	11 (10.6-13)	0.39
Serum albumin levels (mg/dl)	2.6 (2-3)	2.6 (2-3)	0.944
Serum total protein (mg/dl)	8 (7-8)	8 (7-8)	0.599
A/G ratio	0.95 (0.8-1)	0.95 (0.8-1)	0.957
ESR	87.5 (67-110)	87 (66-100)	0.853
Comorbids			
Diabetes	7 (7.5)	86 (92.5)	0.583
Hypertension	6 (6.7)	83 (93.3)	0.406
Hyperparathyroidism	1 (2.8)	35 (97.2)	0.197

complications of myeloma.[4] Its management remains challenging. Cast nephropathy is the most common cause of severe kidney dysfunction in multiple myeloma.[7] At the time of diagnosis, almost 50% of the myeloma cases have significantly decreased kidney function.[8,9,13] Shaheen et al. also revealed that 35% of the myeloma patients had renal impairment (serum creatinine>2 mg/dl) at the time of diagnosis.[5] Even after the advancement in treatment options, still the precise mechanisms for the development of myeloma in patients with kidney disease is incompletely understood.[3,14-18] Hence, in the current study, we have evaluated the frequency and clinical features of myeloma along with socio-demographic factors among patients with chronic kidney disease.

Globally, median age at the time of diagnosis is 70 years.[3] In the current study, myeloma was diagnosed in 14 patients with chronic kidney disease. Among them, 8 cases had stage 4-5 chronic kidney disease. We found the median age of our patients with myeloma was 53.5 years. In other studies, by Soleymanian et al. and Kyle et al., myeloma was frequently present among patients of older age and median age at the time of diagnosis was 59-66 years.[19,20] While, Ludwig et al. found median age at the time of diagnosis as 70 years.[21] In another similar Indian study by Devi et al., the mean age of myeloma patients was 58.8 years.[22] Moreover, we found proportion of myeloma was higher among males than females, which is similar to the previous studies by Soleymanian et al. and Shaheen et al.[19,23] Basharat et al. also reported most of the patients with myeloma were males (73%).[5]

The most frequent comorbid in our patients with myeloma and chronic kidney disease was diabetes. Hence, the patients with chronic kidney disease had higher risk of myeloma if they were diabetic. At the time of diagnosis, almost 50% of the myeloma cases have significantly decreased kidney function (*estimated glomerular filtration rate* less than 60 mL/minute/1.73m^2), with 10 to 15% needing hemodialysis and approximately 1% progressing to end-stage kidney disease.[8,9] In the current study, all the patients with myeloma were anemic with median hemoglobin level as 8.45 gm/dl, which contributes mainly to fatigue and weakness. Whereas, in other studies, the frequency of anemia was reported as 73 to 88%.[19,20] Basharat et al. found that 93% of the myeloma patients had anemia. Kaur et al. also found that 88% of the patients with multiple myeloma had hemoglobin level less than 12 mg/dl.[24] Kyle et al. showed that 73% of the myeloma patients had normocytic normochromic anemia at presentation.[20] In patients with myeloma, anemia can be analogous to kidney dysfunction, bone marrow replacement or can be due to dilution in the case of huge M-protein. Therefore, it was anticipated that kidney failure in myeloma patients with chronic kidney disease would frequently be caused by hypercalcemia, which is also a common consequence of anemia.[19] In our study, we also found patients with myeloma and chronic kidney disease had lower level of serum calcium. According to Kyle et al. 28% of the myeloma patients had hypercalcemia.[20] Monoclonal protein binding with calcium may be because of increase in serum calcium.[5]

Despite efforts to control confounding factors, there are a number of limitations in the present study. The sample size of the study was small and it was a single center study. Therefore, findings cannot be generalized to entire population. The design of the study was cross-sectional that's why we were unable to identify the cause-effect relationship between myeloma, chronic kidney disease and comorbids. In future, prospective studies with larger sample sizes should be done in order to increase the generalizability of findings.

CONCLUSION:

Frequency of myeloma among patients with chronic kidney disease was low. Hence, renal impairment in patients with multiple myeloma is a common complication that worsen the prognosis of the disease. Treating early and effectively with new chemotherapy drugs can stop or delay the progression of disease and improve survival outcomes

Authors Contribution:
Farzana Rashid: Conception, design, literature review, critical review, Final approval of manuscript
Syed Tajammul Ali: Conception, design, literature review, critical review, Final approval of manuscript
Sidra Rashid: Methodology, discussion, Final approval of manuscript
Mehwish Qamar: Interpretation of results, critical review, Final approval of manuscript
Khadijah Abid: Data analysis and drafting of manuscript, Final approval of manuscript

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