CORRELATION OF DEMOGRAPHIC VARIATIONS WITH STAGING OF MULTIPLE MYELOMA PATIENTS IN THE KURDISTAN REGION OF IRAQ

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ABSTRACT

Background

Multiple myeloma is a malignant proliferation of a single clone of plasma cells that produces monoclonal proteins. It is one of the most frequently diagnosed haematological malignancies.

Objectives

To explore the epidemiologic and demographic characteristics of multiple myeloma patients in this area and to study their relationship with the stage of the disease.

Subject and Methods

In this retrospective study, 176 multiple myeloma patients from the three governorates of the Iraqi Kurdistan region were diagnosed from June 2013 to December 2018. Their demographic and clinical characteristics and their laboratory and radiological results were analyzed and correlated with the disease stage.

Results

The patients' median age at diagnosis was 61 years with a range of 35-89 years. The male to female ratio was 1.37:1. The majority of patients were of low social status from the urban areas. Bone pain was the most common presenting symptom encountered in 79% of patients. At the time of diagnosis, anaemia, pathological fractures, renal impairment, and infections were encountered in 62.55%, 21%, 19.9%, and 4.5%, respectively. At the time of diagnosis, 50.6% of the patients had stage II disease, 36.9% had stage III, and 12.5% had stages I disease. The demographic features did not have any significant relation with the stage of the disease.

Conclusion

Multiple myeloma patients in our locality are younger than what has been so far reported from the western world. Half of our cases presented with stage II disease.

Keywords: *Multiple myeloma; Renal impairment; Pathological fracture; Iraqi Kurdistan.*

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INTRODUCTION

Multiple myeloma (MM) is the clonal expansion of plasma cells that secrete a monoclonal M-protein. It accounts for about 1% of all malignancies, 10-15% of haematological malignancies, and an estimated 20% of death from haematological malignancies [1]. The median age at diagnosis is about 70 years; 90% of cases occur in more than 50 years old, 15% of cases are diagnosed in those below 50 years, and only 2% are encountered below the age of 40 years. MM is subtle in those <30 years old with a range of 0.02% to 0.3%; it is seldom seen in the pediatric age group [2, 3]. MM is more common in the industrialized western countries in Europe and the USA; this is probably attributed to better access to health services and better diagnosis than the rest of the world, where fewer incidence rates are reported [4].

The etiological risk factors are not well understood, but there is a high incidence among older age, male gender, family history, and black race. Occupations mainly farming, exposure to pesticides, solvents, especially benzene, other chemicals, and hair dyes have shown a higher risk of myeloma. Nearly all patients are preceded with monoclonal gammopathy of undetermined significance (MGUS) before the overt disease [3,5]. Current data suggest that smoking can be a slight risk; alcohol is not closely related to myeloma development, relative decrease with a diet rich in fruit and vegetables. Multiple epidemiologic studies support obesity as a risk factor; some data suggest increased risk among HIV and HCV-infected persons [4].

MM may present with varying clinical presentations ranging from asymptomatic to aggressive and life-threatening conditions. However, in most cases, the clinical features are due to myeloma-related end-organ damage (CRAB), including hypercalcemia, renal impairment, anaemia, and lytic bone lesions [6].

The diagnosis of MM requires the presence of >10% plasma cells in the bone marrow or tissue biopsy with the presence of end-organ damage (CRAB). In 2014, the international myeloma working group (IMWG) added three specific criteria for those plasma cell disorders which do not show end-organ damage: (i) clonal plasma cell in the bone marrow ≥60% (ii) serum free light chain ratio ≥100, and (iii) >1 focal lesion on MRI measuring ≥5 mm. They also allow CT or PET/CT to diagnose MM bone disease. These new criteria help early diagnosis and start treatment impede end-organ damage in high-risk patients [7].

The exact staging for newly diagnosed myeloma to determine the tumour burden and decide on a treatment plan and prognosis is crucial. In 1975 Durie- Salmon staging system classified MM into three groups depending on laboratory findings, radiological findings on conventional radiography, and amount of M-protein on serum protein electrophoresis (SPE). However, this staging has some limitations as conventional radiography can detect bone lesions when there is a loss of about 30-50% of its density and cannot detect the activity of the lytic lesions. Therefore, in 2005 a new international scoring system (ISS) was developed, which depends on β2 microglobulin and classifies patients into three groups [8]. In 2015, the International Myeloma Working Group (IMWG) introduced the revised ISS that added serum lactate dehydrogenase (LDH) and cytogenetic abnormality detected by FISH to the ISS system [9]. Table 1 illustrates the progress of the MM staging system.

Information and data about MM are scarce in this region. In addition, little data is available about the disease characteristics in this area. Therefore, we deemed it necessary to study the demographic and clinical features of MM patients in this region and correlate them with the stage of the disease at the time of diagnosis.

Table 1. illustrates the progress of the MM staging system [10].

Stage	Durie-Salmon Staging	International Staging System	Revised International Staging System
I	Hemoglobin > 10.5g/dL Calcium ≤ 12mg/dL IgG < 5g/dL; IgA < 3g/dL Bence Jones < 4g/24hrs Bone x-ray: normal or Solitary bone Plasmacytoma	β2microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL	β2-microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL plus normal LDH and no high-risk cytogenetics
II	Neither I nor III A: Creatinine ≤ 2mg/dL B: Creatinine > 2mg/dL	Neither I nor III	Neither I nor III
III	Hemoglobin < 8.5g/dL Calcium > 12mg/dL IgG > 7g/dL; IgA > 5g/dL Bence Jones > 12g/24hrs Bone x-ray > lytic lesions	β2-microglobulin ≥ 5.5 mg/L	β2-microglobulin ≥ 5.5 mg/L and elevated LDH or high-risk cytogenetics [t(4;14), t(14;16), or del(17p)]

***Abbreviations: LDH, lactate dehydrogenase; MM, multiple myeloma.**

MATERIAL AND METHODS

In this study, a total of 176 MM patients diagnosed in the period from June 2013 to December 2018 were retrospectively included in this analysis. They were registered in the three Hemato-Oncology centres of the Iraqi Kurdistan region, Erbil (62 patients), Duhok (22 patients), and Sulaymaniyah (92 patients). The diagnosis of the included patients was based on the presence of >10% plasma cells in the bone marrow, or tissue biopsy with the presence of one or more CRAB features according to IWMG [9]. Patients with incomplete data were not included in this study. Moreover, cases with isolated plasmacytoma of the bone, monoclonal gammopathy of undetermined significance (MGUS), smouldering myeloma, and amyloidosis were also excluded. Data were retrieved from the patients' records. All patients had full haematological and biochemical investigations, radiological examinations, serum and urine protein electrophoresis with immune fixation, bone marrow aspiration, and biopsy. Not all patients had MRI, PET/CT scans, LDH, and β2 microglobulin at the time of diagnosis. Performance status was assessed according to the ECOG grading system [11]. Socioeconomic status was scored according to the modified (SLI) scoring system [12]. The study was approved by the research ethics committee of the Kurdistan Board for Medical Specialties (KBMS), Erbil, Iraq.

Statistical analysis was performed using the statistical package for the social sciences (version 22.0). Quantitative data were described using mean, standard deviation, median, and range. A Chi-square test was used to compare categorical data. Significance was considered at $P < 0.05$.

RESULTS

The patients' age at diagnosis ranged from 35 to 89 years, with a median of 61 years. The male to female ratio was 1.37:1. Although farmers constituted 8.5% of the patients, only one patient had a history of exposure to benzene products. The BMI was higher than average in 63.1% of the patients. Two-third of the patients were residents of urban areas. Those with ECOG 0-1 performance state were 68 (38.6%), and 108 (61.4) had ECOG. ≥2. The detailed patients' demographic characteristics are illustrated in Table 2.

Regarding clinical presentation, 139 (79%) patients presented with bone pain, 125 (71%) had fatigue, 110 (62.5%) were anemic (mean hemoglobin 10.009 gm/dl), pathological fractures were encountered in 37 (21%) patients, renal impairment was observed in 35

(19.9%) patients, hypercalcemia was found in 16 (9.1%) and 8 patients (4.5%) presented with infections. IgG secreting myelomas were the commonest, 119 (67.6%) patients, followed by IgA in 28 (15.9%) patients, while 16 (9.2) patients had non-secretory myelomas and 13 other (7.3%) had light chain type. Table 2 shows the demographic and clinical characteristics of the patients.

Tables 3 and 4 show staging of MM patients at the time of diagnosis according to both Durie-Salmon and ISS staging. The tables reveal the relation of the disease stage to the different demographic parameters. The ISS stage could not be defined in 43 patients due to a lack of data. No relation between the disease stages at presentation was found with almost all studied parameters apart from the patients' residence, which revealed significant relation with Durie-Salmon staging. Patients <40 years mainly had stage I disease.

The staging of disease compared with median and mean ages and BMI s by Kruskal Wallis tests; Statistical analysis shows no difference between staging with age and BMI, Table 5 ,6.

Table 2. Demographic and clinical data of 176 patients with MM in Iraqi Kurdistan

Categories	Frequency	%
Age groups (year)		
<40	6	3.4
40-49	23	13.1
50-59	54	30.7
60-69	54	30.7
≥70	39	22.2
Gender distribution		
Male	102	58.0
Female	74	42.0
Occupation distribution		
Benzene worker	1	0.6
Farmer	15	8.5
Others	160	90.9
Socio-economic status		
High	23	13.1
Middle	68	38.6
Low	85	48.3
Residency		
Rural	58	33.0
Urban	118	67.0
BMI		
<18.5	4	2.3
18.5-24.9	61	34.7
25-29.9	69	39.2
≥ 30	42	23.9
Presenting symptom		
Fatigue	139	79.0
Bone pain	125	71.0
anemia	110	62.5
Pathological fracture	37	21.0
Renal involvement	35	19.9
Hypercalcemia	16	9.1
Infection	8	4.5
Others	15	8.9

Table 1. Continued...

Categories	Frequency	%
Type of protein		
IgG	119	67.6
IgA	28	15.9
Non-secretory	16	9.2
Light chain	13	7.3
Total	176	100.0

Table 3. Durie-Salmon disease stage in relation with patients' demographics.

		Stage I	Stage II	Stage III	p-value
		22 (12.5%)	**89(50.56%)**	**65 (36.9%)**	
Age	<40	2 (1.13)	4 (2.27)	0	**0.11**
	40-49	4 (2.27)	14 (7.95)	5 (2.84)	
	50-59	3 (1.70)	28 (15.90)	23 (13.06)	
	60-69	8 (4.54)	21 (11.93)	25 (14.20)	
	≥70	5 (2.84)	22 (12.50)	12 (6.81)	
Gender	Male	13 (7.38)	53 (30.11)	37 (21.02)	**0.198**
	Female	9 (5.11)	36 (20.45)	29 (16.48)	
Residence	Urban	13 (7.38)	68 (38.63)	37 (21.02))	**0.027**
	Rural	9 (5.11)	21 (11.93)	28 (15.90)	
Socioeconomic	High	2 (1.13)	10 (5.68)	11 (6.25)	**0.28**
state	Middle	5 (2.84)	38 (21.59)	25 (14.20)	
	Low	15 (8.52)	40 (22.72)	30 (17.04)	
BMI	Underweight	0	2 (1.13)	2 (1.13)	**0.91**
	Normal	8 (4.54)	57 (32.38)	39 (22.16)	
	Overweight	14 (7.95)	57 (32.38)	39 (22.16)	

Table 4. ISS disease stage in relation with patients' demographics

		Stage I	Stage II	Stage III	p-value
		30(22.5%)	61(45.8%)	42(31.57%)	
Age	<40	4 (3.00)	0	0	**0.05**
	40-49	4 (3.00)	8 (6.01)	5 (11.9)	
	50-59	6 (4.51)	18 (13.53)	14 (10.52)	
	60-69	10 (7.51)	19 (14.28)	12 (9.02)	
	≥70	6 (4.51)	16 (12.03)	11 (8.27)	
Gender	Male	13 (9.77)	33 (24.81)	29 (21.80)	**0.08**
	Female	17 (12.78)	28 (21.05)	13 (9.77)	
Residence	Urban	18 (13.52)	45 (33.83)	35 (26.31)	**0.08**
	Rural	12 (9.02)	16 (12.03)	7 (5.26)	
Socioeconomic	High	8 (6.01)	8 (6.01)	2 (1.50)	**0.07**
state	Middle	8 (6.01)	28 (21.05)	18 (13.53)	
	Low	14 (10.52)	25 (18.79)	22 (16.54)	
BMI	Underweight	0	2 (1.50)	2 (1.50)	**0.34**
	Normal	5 (3.75)	26 (19.54)	18 (13.53)	
	Overweight	24 (18.04)	33 (24.81)	22 (16.54)	

Table 5. Result of Kruskal Wallis test between Durie-Salmon staging with age and BMI.

	Null hypothesis	Test	Significance	Decision
1	**The distribution is the same across categories of the stage of disease Durie-Salmon.**	Independent Samples Kruskal Wallis Test	0.590	Retain the null hypothesis
2	**The distribution of BMI is the same across categories of the stage of disease Durie-Salmon.**	Independent Samples Kruskal Wallis Test	0.657	Retain the null hypothesis

***The significance level is 0.05.**

Table 6.the result of the Kruskal Wallis test between ISS staging with age and BMI.

	Null hypothesis	Test	Significance	Decision
1	**The distribution is the same across categories of the stage of disease ISS.**	Independent Samples Kruskal Wallis Test	0.319	Retain the null hypothesis
2	**The distribution of BMI is the same across categories of the stage of disease ISS**	Independent Samples Kruskal Wallis Test	0.839	Retain the null hypothesis

***The significance level is 0.05.**

DISCUSSION

MM is conventionally defined as excess monoclonal bone marrow plasma cells in the setting of monoclonal protein in the blood and/or urine. Although rare, it is the second most frequent hematologic neoplasm. The disease has a global annual incidence of approximately 114,500 and an annual mortality of approximately 80,000 [13, 14].

In this study, the median age of our MM patients at the time of diagnosis was 61 years which is considerably lower comparing to the reports from the western world where the median age of patients at diagnosis is approximately 66–70 years with 37% of patients being younger than 65 years of age [3, 6, 15]. MM is extremely rare in those <30 years of age with a reported frequency of 0.02%–0.3% [16]. In the current cohort, 113 patients (64.2%) were younger than 65 years and 6 others (3.4%) were younger than 40 years. These figures are comparable to data from Iran and Turkey [17, 18] and very similar to data from a previous local study [19]. The male to female ratio was 1.37:1, it is well known that MM affects men more frequently than women, and its incidence increases with age. MM occurs less frequently in Asian countries than in Western countries [12].

Two-thirds of our patients (67%) were residents of urban areas; a similar finding was reported from Iran[17]. Residents of the urban areas have more exposure to carcinogenic agents and generally have a sedentary lifestyle. Although the exact causes of MM are unknown, some factors have been shown to increase the risk of MM [3, 5]. In this study, 8.5 % were a farmer and being exposed to pesticides, and only one patient had a history of benzene exposure. Like in many other studies, no apparent predisposing factors were found in the majority of cases [20]. Some studies and meta-analyses have reported a relation between MM and obesity [21]. Although 63.1% of our patients were overweight or obese, we cannot confirm a direct relationship between the disease incidence and BMI unless correlated with the BMI of the general population. Previous studies have shown that MM is more common within the low socioeconomic group of population [22] in our cohort; the comparable finding was noted as nearly half of patients (48.3%) were from the low socioeconomic group.

The most common patients' presenting symptoms in this study were bone pain (79%), followed by fatigue (71%) and anaemia (62.5%). These results are comparable to many other studies in Iraq and the surrounding countries of Saudi Arabia and Turkey [23, 24] although, in Turkey, anaemia was more frequently encountered at presentation [17, 25]. Pathological fractures were seen in 21% of patients; this is almost similar to the data of Aysun et al. in Turkey [18]. The rate of renal impairment at the time of presentation was slightly lower and detected in 19.9% of our cases; higher rates were reported in Baghdad, Saudi Arabia, Iran, and Turkey [13, 18, 24, 25]. Serum IgG was the most common protein consistent with previously established data [26].

According to the Durie-Salmon staging system, half of our cases (50.5%) had stage II disease, and 36.9% had stage III. A previous local study reported that the majority of MM presented with stage III disease [27]. This may indicate earlier detection of MM with the improvement in the diagnostic tools. Only 133 patients out of 176 had the β2-microglobulin level at the time of diagnosis and were staged according to the ISS scoring system. This test was not available to be done by 44 patients, therefore, were not included in our ISS classification. According to the ISS system, 34.7% of MM patients had stage II, and 23.9% had stage III disease at the time of diagnosis. Dissimilar results have been reported by Ayun et al. and Abdul Hammed et al.[18, 25] who reported high percentages of patients being in stage III. The age of the patients, gender, BMI, and socioeconomic status did not relate with the stage of MM at the time of presentation. In our study, 38.6% of our patients had an ECOG performance of 0-1, while 61.4% had ≥ 2 ECOG performance scale. Unlike our results, two separate studies in the USA and France [28, 29] reported that most of their MM cases had an ECOG score of 0-1.

In conclusion, the median age of our multiple myeloma patients was considerably lower than in the west. The patients were mainly from the lower social class of the urban areas. There was no relation between the stage of the disease and patients' demographic features. Half of the patients had stage II disease at the time of presentation—younger patients presented with earlier disease stages. Bone pain and fatigue were the standard presenting features, with one-fifth having a renal impairment.

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