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RESEARCH PAPER

Clinical Diversity of Multiple Myeloma at the First Presentation through the Time Lapse to Diagnosis in Kurdistan Region, Iraq

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A B S T R A C T:

Multiple myeloma (MM) is a malignancy of the plasma cells. The study aimed to know the clinical diversity of MM at presentation, the time lapse from the first symptoms to diagnosis, and the association of this time lapse with the International Staging System (ISS) of MM. This is a retrospective observational study that was performed on 176 patients who had MM and were admitted to Hiwa Hospital in Sulaimani, Nanakaly Hospital in Hawler, and Azadi Hematology - Oncology Center in Duhok, from October 2010 to December 2019. Demographic and detailed clinical features were recorded, and the ISS of MM was used to assess possible effects of time lapse on patients' outcomes. The mean ± SD (standard deviation) of patients' age was 60.58 ± 11.54 years, and the majority of the patients (52.27%) were from Sulaimani. Most of them had an O+ blood group and a body mass index (BMI) of more than normal (30.68%, and 63.63%, respectively). Most of the patients had bone pain, ≥2 lytic lesions,

hypocalcemia and hypercalcemia, and renal impairment and stage II and III of ISS of MM at the time of diagnosis (78.98%, 32.39%, 49.43%, 89.77%, and 75.1%, respectively). Furthermore, their mean ± SD of time lapse from the first symptom to diagnosis was 3.01 ± 3.18 months, and its association with ISS was none significant. The clinical features of MM at diagnosis are mostly nonspecific, and may be shared by a wide range of clinical conditions. However, patients who have fatigue, bone pain, renal impairment, pallor, and infective events should arouse the clinical suspicion of MM.

KEY WORDS: International Staging System (ISS); Kurdistan; Multiple myeloma; Time lapse
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1. INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells preceded by its asymptomatic premalignant monoclonal gammopathy of undetermined significance (MGUS) (Eslick and Talaulikar, 2013; Shephard et al., 2015; Goldschmidt et al.,2016; Rajkumar, 2018; Koshiaris et al., 2018; Li et al., 2019). The plasma cells proliferate and accumulate in the bone marrow and locally destroy bones due to their secretion of monoclonal paraproteins, which signifies end-organ damage (Eslick and Talaulikar, 2013; Shephard et al., 2015; Goldschmidt et al.,2016; Koshiaris et al., 2018). It represents 1% of all cancers, and 10-20% of all hematological malignancies and its incidence increases with aging (Shephard et al., 2015; Goldschmidt et al., 2016; Rajkumar, 2018; Koshiaris et al., 2018). In the United States, more than 30000 patients per year are diagnosed with MM, the annual age-adjusted incidence is nearly 4 per 100000, and more than 12000 are dying due to this disease (Rajkumar, 2018). Also, MM accounts for 2% of all newly diagnosed cancers with an incidence of 5500 patients per year in the United Kingdom (Li et al., 2019). Multiple Myeloma is slightly more common in males; the male to female ratio is 1.3:1, and it is twice as common in African-Americans as compared with Caucasians (Shephard et al., 2015; Rajkumar, 2018). Moreover, the median of age at diagnosis is 64-65 years, and in adults, it is the second common hematological malignancy (Eslick and Talaulikar, 2013; Shephard et al., 2015; Goldschmidt et al., 2016; Rajkumar, 2018; Koshiaris et al., 2018).

The clinical features of MM are ill-defined and broad, especially the initial symptoms which may be nonspecific and pose difficulties for the patients and the clinicians in differentiating it from prodromes of other self-limiting benign diseases (Howell et al., 2013). Moreover, MM presents with a wide range of symptoms and signs, including anemia, hypercalcemia, renal impairment, bone pains, and increased risk of infection, and any combination of these symptoms should arouse the attention of MM diagnostic evaluation and workup (Eslick and Talaulikar, 2013; Rajkumar, 2018). Bone lesions are the leading cause of morbidity in MM, and characteristically osteolytic bone lesions of MM do not exhibit new bone formations. Further, nearly 1-2% of the patients at the time of diagnosis have an extramedullary disease, and later during the disease course, 8% will also develop it (Rajkumar, 2018).

The diagnosis of MM can be challenging due to the possible extended time between the onset of the symptoms, consulting frequent and different medical professionals, and then the diagnosis (Friese et al., 2009; Howell et al., 2013; Shephard et al., 2015; Howell et al., 2018). Some of the patients are diagnosed after emergency admissions to hospitals with a poorer prognosis (Howell et al., 2013; Friese et al., 2009). This time lapse between the onsets of the symptoms to the diagnosis is important because early diagnosis can improve the outcome, including less complication and decreased mortality, as well as better quality of life and satisfaction with care (Friese et al., 2009; Howell et al., 2013; Neal et al., 2015). Therefore, measures should be taken in order to aware patients and professionals in the primary care units for the sake of early diagnosis (Friese et al., 2009; Howell et al., 2013).

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The diagnostic workup of plasma cell abnormalities is by identifying the presence of monoclonal paraprotein, baseline hematological, and radiological assessments, as well as bone marrow biopsy (Eslick and Talaulikar, 2013). The radiological assessment of bone lesions can be performed through routine radiographs, low dose whole-body computed tomography (CT) scan, magnetic resonance imaging (MRI), and sometimes fluorodeoxyglucose positron emission tomography (PET) scans (Rajkumar, 2018).

The diversity of the clinical features of MM and, therefore, the difference in the time lapse between first symptoms and signs till diagnosis can be managed by educating the patients and medical professionals of the primary health care (Friese et al., 2009; Howell et al., 2013; Neal et al., 2015). Therefore, in the current study, we aimed to know the clinical diversity of MM at presentation, time lapse from the first symptoms to the diagnosis, and the association of this time lapse with the International Staging System (ISS) of patients afflicted with MM in Kurdistan Region, Iraq.

Patients and Methods

The current study is a retrospective observational study that included 176 patients who had MM. The patients were hospital admitted to Hiwa Hematological and Oncological Hospital in Sulaimani, Nanakaly Hospital in Hawler, and Azadi Hematology - Oncology Center in Duhok, Kurdistan Region, Iraq, during the period from October 13, 2010, to December 3, 2019.

Research Ethical Committee of the Kurdistan Board of Medical Specialties (KBMS) approved the study proposal.

The inclusion criteria included all patients who had been diagnosed with MM, and the exclusion criteria were patients with MGUS, amyloidosis, and Smoldering myeloma.

The recorded information about the patients was collected from the electronic databases of the mentioned hospitals. The demographic features, including age, gender, body mass index (BMI), residency, and detailed history and clinical features, including the time lapse from the first symptoms and signs, were recorded. Also, the ISS of MM was used to assess the effect of time lapse on the disease outcomes.

The "IBM SPSS Statistics version 25" program was used for the analysis of the data, and both descriptive and inferential statistics were used. Further, means and standard deviation (SD) were used for continuous variables, and frequencies, as well as percentages, were used for categorical variables. Also, the Chi-Square test was used to find out the significance of the association between categorical independent and dependent variable pairs. Besides, a *p*-value of ($\leq$0.05) was considered statistically significant associations.

Results

The mean ± SD (standard deviation) of the patients' age was 60.58 ± 11.54 (ranged from 35 to 89 years), and the majority of the patients were in their fifth and sixth decades of life (Figure 1). Also, most of the patients were Kurdish males from the Sulaimani governorate (Figures 2-3). Further,

most of the patients had O+, followed by A+ and B+ blood groups, and a BMI of more than normal (i.e., >25) (Figures 4-5).

The majority of the patients were referred by internal medicine, orthopedics, followed by rheumatology and neurosurgery specialties (Table 1).

Most of the patients had bone pain, fatigue, and pallor (78.98%, 71.02%, and 53.98%, respectively).

Further, other clinical features are shown in Table 2.

The majority of the patients had two or more lytic lesions on skeletal radiographs, which were mostly affected skull, spine, and pelvis (Table 3).

The laboratory findings of the patients' investigation are shown in Tables 4 and 5. Peripheral blood plasma cells presence is shown in Table 6. Besides, the majority of the patients had a hypercellular feature on bone marrow aspiration and biopsy (Table 7). The serum and urine protein electrophoresis, serum and urine

immunofixation assessments of the MM patients at diagnosis are shown in Tables 5 and 8 respectively. Most of the patients had stage II and III of the International Staging of MM at diagnosis (Table 9).
The mean ± SD of time lapse from the first clinical feature to the diagnosis was 3.01 ± 3.18 months (ranged from 0.25 to 18 months). Furthermore, the study results showed statistically none significant association between the time lapse from the first clinical feature to the diagnosis assessed by the International Staging system of MM (Table 10).

Discussion

Multiple myeloma (MM) is a cancer of the plasma cells of the bone marrow and its incidence increases among older ages; the median of age at diagnosis is 64-65 years (Eslick and Talaulikar, 2013; Shephard et al., 2015; Goldschmidt et al., 2016; Rajkumar, 2018; Koshiaris et al., 2018). In contrast, the mean age of the patients in the current study was about 60.6 years old, and the majority of them were in the fifth and sixth decade of their lives (Figure 1). Besides, the population in the developed world is getting older due to the advances in health care and stable lifestyles; the average life span in the west is about 77.5 years (WHO, 2020). However, this slight difference in the ages of the patients may be due to the differences in demographic and genetic backgrounds of our population to theirs.

Previous studies have shown that , MM was more common among males with a male to female ratio of 1.3:1 (Shephard et al., 2015; Rajkumar, 2018). And although a slightl increase in the frequency of MM in males was comparatively observed in the current study, however the results were almost about the same; with a male to female ratio of 1.4:1 (Figure 2).

A study by Ino-Ekanem et al. (2018) in Nigeria showed no significant association between hematological cancers and ABO blood type of patients, although most of their patients had O blood type. Further, patients with MM had group III ABO discrepancies, i.e., discrepancies between forward and reverse groupings due to protein or plasma abnormalities that result in the rouleaux formation or pseudo-agglutination (Wilson and Jacobs, 2002). Therefore, ABO blood types are not reliable predictors for the diagnosis of MM, although most of our patients had group O followed by group A and group B (Figure 4).

Significantly increased body weight has been identified as a risk factor for many malignant tumors. The majority (63.6%) of the patients in the current study had a BMI of more than normal (Figure 5). This finding is in accordance with the finding of the meta-analysis performed by Wallin et al., 2011), who found excessive body weight as a risk factor for MM.

The clinical features of MM are nonspecific and diverse in such a way that thay usually pose difficulties in diagnosis, and the patients may seek different specialties to manage their suffering (Howell et al., 2013). This may be the reason in the current study for the referral of the patients by different specialties (Table 1). Besides, the majority of this study's patients complained of fatigue, followed by pallor, bone pain and pathological fractures, renal impairment and hypercalcemia, and infective events (Table 2). These symptoms were considered as arousal signals for suspecting MM in the literature (Eslick and Talaulikar, 2013; Rajkumar, 2018). Moreover, bone pain and pathological fractures are due to the osteolytic bone lesions that do not show new bone formation (Rajkumar, 2018). The radiographic bone scans of our patients showed about the same; the majority of our patients were afflicted with lytic bone lesions and osteopenia that caused multiple bone fractures (Table 3). The fractures of the bones had been suggested to be due to the proliferation and accumulation of the plasma cells and its secretion of monoclonal paraprotein in the bone marrow of the bones that are hematopoietically active in adults, such as vertebrae, ribs, and sternum, skull, pelvis, proximal epiphyseal regions of femur and humerus bones (Shephard et al., 2015; Koshiaris et al., 2018).

Most of the laboratory results of our patients showed anemia, renal impairment, high Beta-2 microglobulin, high ESR, leukocytosis, hypercalcemia, and bone marrow plasma cells (Tables 4 and 5). Peripheral blood plasma cells were not detected in 130 (73.86%) of the study patients and were present in 46 (5.11%) of them (Table 6). These laboratory findings were in accordance with the laboratory findings of previous studies (Eslick and Talaulikar, 2013;

Willrich MA, Katzmann, 2016; Rajkumar, 2018; Chowdhury, 2018; Hussain et al., 2019).

Further, most of the patients had hypercellularity on bone marrow aspiration and biopsy (Table 7) due to plasma cell proliferation in bone marrow (Eslick and Talaulikar, 2013; Shephard et al., 2015; Goldschmidt et al., 2016; Rajkumar, 2018; Koshiaris et al., 2018; Li et al., 2019). Also, the majority of the patients had high serum and urine IgG of 51.71% and 29.54%, respectively (Table 8). These findings were also in accordance with the study of Willrich et al. (2016) in which they found 52% of IgG in their patients who were diagnosed with MM.

We used ISS for the classification of MM in the patients, and the majority of the patients had grade II followed by grade III and grade I (Tables 9 and 10). These results were different from the results found by Goldschmidt et al. (2016), who could calculate the ISS for only 43 of their patients; the majority of their patients had grade I followed by grade II and grade III. However, the study of Byun et al. (2019) showed that the majority of their patients were in grade II followed by grade I and grade III. These differences in the frequencies of the stages of MM according to the ISS may be due to the differences in the study populations and the variability of the time lapse from the first symptom and sign to the diagnosis. Although the majority of the patients who had ISS stage II followed by stage III were diagnosed within five consecutive months' time lapse from the start of symptoms to the diagnosis, the association of this time lapse with the staging of MM was statistically none significant (Table 10). Besides, the majority of patients (85.5%) were diagnosed within five months from the first symptom, with an average of 3.01 months (about 91 days) (Table 10). This time lapse is less than what had been found in the study of Howell et al. (2013), who found an average time lapse of 163 days (about 5.4 months) from the first symptom to the diagnosis of MM. As it is shown in Table 10, this time lapse was quite variable and dispersed, and this may be the reason that its association with MM staging was not statistically significant.

Table (1): The clinical units where the MM patients referred from

The clinical area referred from	Frequency	Percent
Rheumatology	26	14.77
Neurosurgery	19	10.80
Internal medicine	42	23.86
Neuro-Medicine	2	1.14
Gynecology	2	1.14
Orthopedic	43	24.44
General surgery	2	1.14
Nephrology	10	5.68
Him/Herself	2	1.14
Cardiology	2	1.14
Oncology	2	1.14
Outpatient consultation	23	13.7
Total	176	100

Table (2): The clinical features of the MM patients

Clinical features	Frequency	Percent
Fatigue	125	71.02
Pallor	95	53.98
Bone pain	139	78.98
Pathological fracture	37	21.02
Renal involvement	36	20.46
Hypercalcemia	16	9.09
Infective event	8	4.55
Weight loss	3	1.70
Multiple vertebral bone lesion	2	1.14
Throat mass	1	0.57
Hepatomegaly	1	0.57
Portal vein thrombosis	1	0.57
Melena and weight loss	1	0.57
Pleural effusion	1	0.57
Advanced osteoporosis with multiple lytic lesion	1	0.57
Excessive sweating	1	0.57
Cervical lymphadenopathy	1	0.57
Joint pain	1	0.57

Table (3): Radiographic findings of the MM patients

Radiological findings		Frequency	Percent
Lytic lesion		108	61.36
Osteopenia		45	25.57
Extraoseous plasmacytoma of tonsil		1	0.57
Degenerative change with disc prolapse		1	0.57
Lumbosacral spine and right radius bone plasmacytoma		1	0.57
Osteoporosis		3	1.70
Frequency of bone lesion	0	28	15.91
	1	42	23.86
	2	36	20.45
	>2	56	31.82
	>3	1	0.57
Site of Bone lesion	Spine	53	30.11
	Skull and spine	28	15.91
	Skull	10	5.68
	Skull and pelvis	5	2.84
	Skull, spine, and pelvis	12	6.8
	Pelvis and spine	12	6.8
	Spine and thoracic cage	4	2.27
	Pelvis	4	2.27
	Skull, spine, and humerus	3	1.70
	Skull, spine, and femur	2	1.14
	Femur	2	1.14
	Not recorded	41	23.30

Table (4): Laboratory hematological findings of the MM patients

Investigation results		Frequency	Percent
Hemoglobin (g/dl)	Mean ± SD (range)	10.01 ± 2.07 (4.9 to 16)	
	Anemia	155	88.07
Mean cell volume (MCV) in fL		90.4 ± 53.73 (8.4 to 769)	
White blood cell (WBC) (10*9 cell/L)	Mean ± SD (range)	7.66 ± 5.54 (2.3 to 54)	
	Leukopenia (< 4)	26	14.77
	Normal (4 - 11)	126	71.59
	Leukocytosis (>11)	24	13.64
Platelet (10*9 cell/L)	Mean ± SD (range)	211.09 ± 91.14 (13 to 615)	
	Thrombocytopenia (<150)	37	21.0
	Normal (150-450)	134	76.1
	Thrombocytosis (>450)	5	2.8
Erythrocyte sedimentation rate (ESR) (mm/hr)	Mean ± SD (range)	92.65 ± 40.92 (3 to 162)	
	Normal	7	3.98
	High	160	90.91
	Unknown	9	5.11
Bone marrow aspiration plasma cell	Mean ± SD (range)	35.45 ± 20.08 (4 to 85)	
Bone marrow biopsy plasma cell	Mean ± SD (range)	45.14 ± 21.99 (0 to 97)	

SD = Standard deviation

Table (5): Laboratory Biochemical and Metabolic findings of the patients

Investigation results		Frequency	Percent
S.Creatinine (mg/dl)	Mean ± SD (range)	1.83 ± 2.94 (0.1 to 31)	
	Low	9	5.11
	Normal	96	54.54
	High	71	40.34
B.Urea (mg/dl)	Mean ± SD (range)	52.77 ± 34.38 (2.6 to 200)	
	Low (<7)	5	2.84
	Normal (7-20)	13	7.39
	High (>20)	158	89.77
$S.Ca^{++}$ (mg/dl)	Mean ± SD (range)	10.03 ± 6.39 (4.4 to 90)	
	Low (<8.6)	44	25.00
	Normal (8.6-10.2)	89	50.57
	High (>10.2)	43	24.43
Total serum protein (g/dl)	Mean ± SD (range)	7.97 ± 2.34 (0.4 to 13.6)	
	Low (<6)	25	14.20
	Normal (6-8.3)	86	48.86
	High (>8.3)	65	36.93
S.Albumin (g/dl)	Mean ± SD (range)	3.91 ± 3.4 (1.9 to 36)	
	Low (<3.4)	74	42
	Normal (3.4-5.4)	98	55.7
	High (>5.4)	4	2.27
Beta-2 microglobulin (µg/mL)	Mean ± SD (range)	6.7 ± 25.64 (0.4 to 340)	
	Normal (0-3)	55	31.3
	High (>3)	118	67
	Unknown	3	1.7
Lactate Dehydrogenase (U/L)	Mean ± SD (range)	296.58 ± 171.46 (4.2 to 1055)	
	Low (<140)	26	14.77
	Normal (140-280)	53	30.11
	High (>280)	80	45.45
	Unknown	17	9.66
Serum uric acid (mg/dL)	Mean ± SD (range)	10.14 ± 30.67 (1.09 to 341)	
	Low	9	5.11
	Normal	78	44.32
	High	46	26.14
	Unknown	43	24.43
Serum protein electrophoresis (g/dL)	Mean ± SD (range)	2.86 ± 2.69 (0 to 24)	
Urine protein electrophoresis (mg/dL)	Mean ± SD (range)	57.12 ± 116.28 (0 to 970)	

SD = Standard deviation

Table (6): Peripheral blood plasma cells

Status:	Frequency	Perecent
Present:	46	5.11%
Absent:	130	73.86 %

Table (7): Bone marrow cellularity findings on aspiration and biopsies

Bone marrow cellularity	Frequency	Percent
BM aspiration cellularity		
Normocellular	46	26.14
Hypercellular	78	44.32
Hypocellular	6	3.41
Diluted	5	2.84
Not done	41	23.30
BM Biopsy cellularity		
Normocellular	34	19.32
Hypercellular	114	64.77
Hypocellular	4	2.27
Not done	24	13.64

Table (8): Immunofixation of patients' serum and urine

Immunofixation at diagnosis	Frequency	Percent
Serum immunofixation		
IgG	11	6.25
IgG and kappa	56	31.82
IgA and kappa	10	5.68
IgA and lambda	16	9.09
Kappa	6	3.41
IgG and lambda	23	13.07
Negative	15	8.52
Lambda	3	1.70
IgG, IgA and kappa	1	0.57
IgM and kappa	1	0.57
Unknown	34	19.32
Urine immunofixation		
IgG	4	2.27
IgG and kappa	32	18.18
IgA and kappa	4	2.27
IgA and lambda	7	3.98
Kappa	13	7.39
IgG and lambda	15	8.52
Negative	41	23.30
Lambda	6	3.41
IgG, IgA and kappa	1	0.57
IgM and kappa	1	0.57
Lambda and biclonal	1	0.57
Not done	51	28.98

Table (9): Multiple myeloma staging of the MM patients

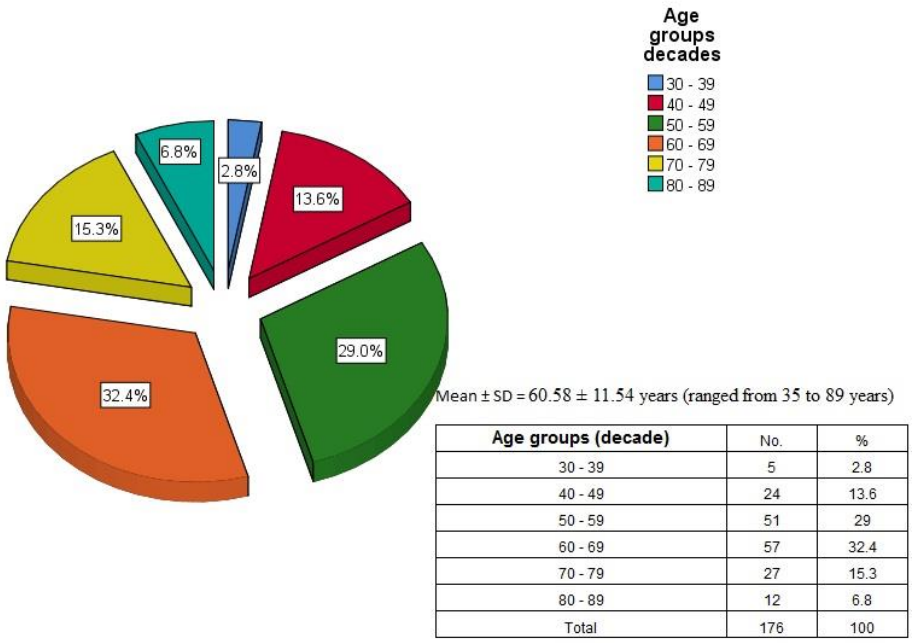
International Staging	Frequency	Percent
I	41	23.3
II	77	43.8
III	55	31.3

Unknown	3	1.7
Total	176	100

Table (10): Association of time lapse to the outcome assessed by the International Staging System

Time lapse to diagnosis (month)	International Staging of multiple myeloma			Total (%)	*p*-value*
	Stage I (%)	Stage II (%)	Stage III (%)		
0.25 - 5	34 (19.7)	71 (41)	43(24.9)	148 (85.5)	
6-10	5 (2.9)	4 (2.3)	8(4.6)	17 (9.8)	
12	1 (0.6)	2 (1.1)	2(1.1)	5 (2.9)	0.349
18	1 (0.6)	0 (0)	2(1.1)	3 (1.7)	
Total	41 (23.7)	77 (44.5)	55(31.8)	173 (100)	

* Measured by Chi-Squared test



Age groups (decade)	No.	%
30 - 39	5	2.8
40 - 49	24	13.6
50 - 59	51	29
60 - 69	57	32.4
70 - 79	27	15.3
80 - 89	12	6.8
Total	176	100

Figure 1: Age distribution of the MM patients

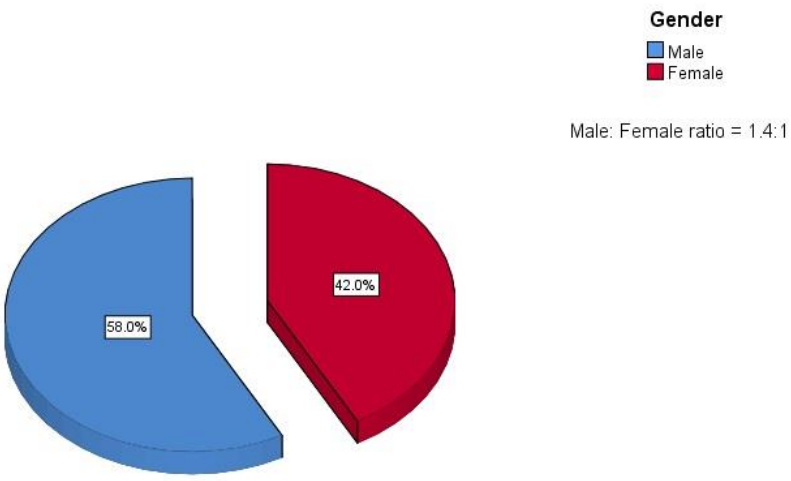


Figure 2: Gender distribution of the MM patients

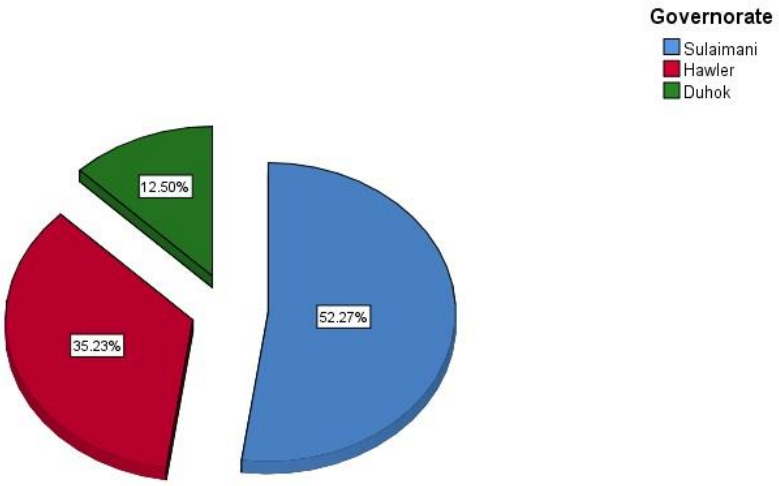


Figure 3: Residency of the MM patients

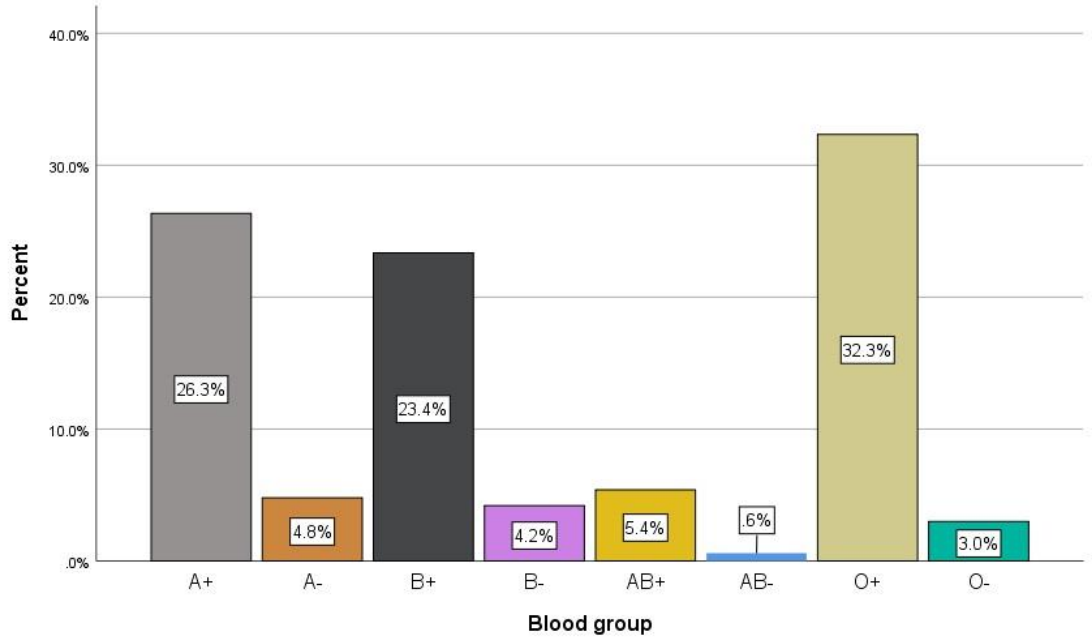
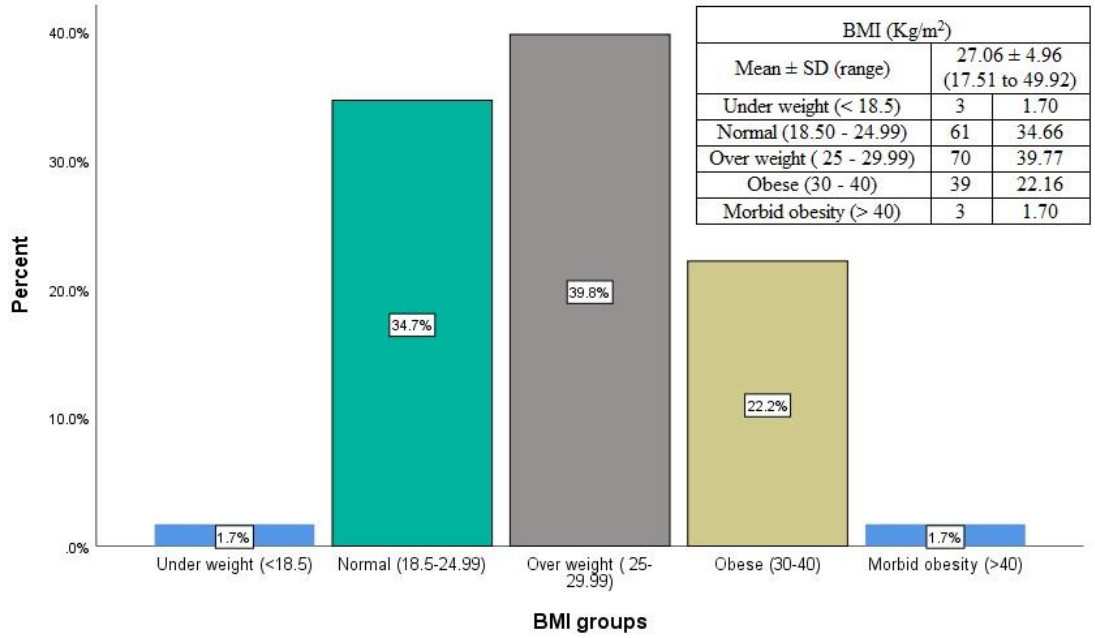


Figure 4: Blood groups distribution of the MM patients



BMI (Kg/m^2)		
Mean ± SD (range)	27.06 ± 4.96 (17.51 to 49.92)	
Under weight (< 18.5)	3	1.70
Normal (18.50 - 24.99)	61	34.66
Over weight (25 - 29.99)	70	39.77
Obese (30 - 40)	39	22.16
Morbid obesity (> 40)	3	1.70

Figure 5: Body mass index (BMI) distribution of the MM patients

Conclusions

The clinical features of multiple myeloma (MM) are broad and nonspecific, which makes its diagnosis difficult. Furthermore, any patient who had fatigue, bone pain, renal impairment pallor, and infective events should arouse the possibility of MM diagnosis. We found no significant association of the time lapse from the first symptom with the stages of MM, and we have the shortage of following the patients up after their treatment. Therefore, we suggest following up on the patients in order to know the effect of this time lapse on the patients' outcome after treatment

Conflict of interest

The authors declare no conflict of interest.

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