

# Frequency and Prognostic Significance of Hypercalcemia in Patients with Multiple Myeloma

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## Abstract

**Background:** Multiple myeloma (MM) is defined as a clonal B-cell malignancy of the bone marrow. Hypercalcemia is associated with cancers in general and in MM specifically becomes more obvious with frequent adverse outcomes. **Objectives:** The objective is to determine the frequency of hypercalcemia in MM patients and survival rate after 3 years of diagnosis with the assessment of relationship between MM prognosis and hypercalcemia. **Materials and Methods:** Retrospective data were reviewed from the Hematology and Cancer Centers of Kurdistan Region of Iraq (KRI, Erbil, Sulaymaniyah, and Duhok) from January 2012 to December 2017 on a sample of 130 patients with MM. The diagnosis of MM and hypercalcemia was done according to the International Myeloma Working Group definition of MM and serum calcium of  $\geq 11$  mg/dl. **Results:** The prevalence of hypercalcemia among MM patients after calcium correction was 17.7%. Serum creatinine level is significantly higher among MM patients with hypercalcemia. There was a significant association between high death rates and MM patients with hypercalcemia. The mean survival of MM patients was 4.5 years and 72% of the MM patients had 3-year survival, which decreased to <41% for 6-year survival. The survival of MM patients with hypercalcemia was significantly shorter than survival of patients without hypercalcemia. **Conclusions:** The frequency of hypercalcemia among MM patients in KRI is within the international acceptable range and is regarded as a poor prognostic factor that is associated with higher mortality and shorter survival.

**Keywords:** Hypercalcemia, multiple myeloma, survival

## INTRODUCTION

Multiple myeloma (MM) is defined as a clonal B-cell malignancy of the bone marrow accompanied by different clinical features, such as renal failure, skeletal disorders, anemia, and infection.<sup>[1]</sup> MM represented 1% of all recorded cancers globally, and it is the second most common hematologic malignancy after lymphoma with an age-specific incidence rate of 32.6%.<sup>[2,3]</sup> The epidemiological features in Kurdistan Region of Iraq (KRI) showed equal male to female affected by MM with predominant backache, bone pain, and anemia.<sup>[4]</sup>

The clinical presentation of MM is commonly caused by the effect of plasma cells on the bone or kidney. However, in some cases, the clinical presentation is nonspecific.<sup>[5]</sup> Recent updated diagnostic criteria for MM as described by the International Myeloma Working Group (IMWG) included

three specific biomarkers essential for diagnosis of MM in the absence of specific clinical features; clonal bone marrow plasma cells ( $\geq 60\%$ ), serum-free light chain ratio ( $\geq 100$ ), and more than one focal lesion on magnetic resonance imaging. In addition, computerized tomography (CT) and positron emission tomography-CT are important in early diagnosis of MM bone diseases.<sup>[6]</sup> MM treatment is dependable on patient

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physical status and health. In patients less than 65 years of age who are eligible for transplantation, MM treatment includes immunomodulatory drug (IMiD) and proteasome inhibitor (PI) in combination with glucocorticoids, followed by autologous stem-cell transplantation and maintenance therapy with low-dose IMiD or PI.<sup>[7]</sup>

Bone destruction present in 80% of MM patients leads to severe bone pain, pathologic fractures, spinal cord compression, and hypercalcemia. The hypercalcemia is recorded in about one-third of MM patients.<sup>[8]</sup> The main etiology of hypercalcemia in MM is the widespread tumor-induced bone destruction, which is related to elevated osteoclastic bone resorption caused by potent cytokines expressed or secreted locally by the myeloma cells or over-expressed by other cells in the local microenvironment that in turn leads to efflux of calcium into the extracellular fluid.<sup>[9]</sup> The relationship between hypercalcemia and MM patients with poor prognosis is still unclear but may attribute to increased amount of bone-resorbing activity, severe renal insufficiency, and higher plasma cell leukemia.<sup>[10,11]</sup>

Hypercalcemia among patients with MM is accompanied with lower prognosis rates globally.<sup>[12,13]</sup> For that, our study aimed to measure the frequency of hypercalcemia in MM patients and survival rate after 3 years of diagnosis with the assessment of relationship between MM prognosis and hypercalcemia.

## MATERIALS AND METHODS

### Study design and patients

This study is a retrospective study with data reviewed and collected in Hematology and Cancer Centers of KRI (Erbil, Sulaymaniyah, and Duhok, Iraq) from January 1, 2012, to December 31, 2017, on a sample of 130 patients with MM.

Inclusion criteria for selected sample were confirmed by the diagnosis of MM according to the IMWG diagnostic criteria, symptomatic patients with availability of full data of complete frequent visits to Hematology and Cancer Centers of KRI. The exclusion criteria were asymptomatic patients (smoldering myeloma, localized plasmacytoma) with amyloidosis and monoclonal gammopathy of undetermined significance.

The saved data were collected by the researcher from KRI including Erbil, Sulaymaniyah, and Duhok cancer centers and hospitals. The questionnaire included age (<60 and ≥60 years), gender (male or female), the Eastern Cooperative Oncology Group (ECOG) score (0–1 or ≥2), anemia defined by hemoglobin <10 gm/dl (yes or no), serum albumin (<3.5 or >3.5 g/dl) serum creatinine (<2 or ≥2 mg/dl), lactate dehydrogenase (LDH) (normal or higher than upper limit of normal), hypercalcemia (serum calcium >11 mg/dl), Durie-Salmon staging (I–III), International Staging System (ISS) staging (I–III), and current patient status (alive or dead). The investigations implemented for patients were done in Laboratories of Cancer Centers in KRI. The survived patients were followed up retrospectively in general for a duration

of 6 years. The diagnosis of hypercalcemia was done by the researcher in accordance with the IMWG definition of serum calcium of >11 mg/dl.

### Ethical consideration

Ethical considerations were taken in consideration according to the Helsinki Declaration by taking approval of study from Ethical Committee of Kurdistan Board and Cancer Centers authorities in addition to taking in consideration confidentiality of patients' data.

### Statistical analysis

Statistical analysis was carried out using Statistical Package of the Social Sciences software version 22 (SPSS, IBM Company, Chicago, IL 60606, USA). Chi-square test and Fisher's exact test were applied for analyzing the data as suitable. Kaplan–Meier curve was used to assess the survival of MM patients. Level of significance (*P* value) was regarded statistically significant if it was 0.05 or less.

## RESULTS

This study included 130 MM patients with a mean age of 59.3 years and range of 35–89 years. Male patients were more than females with male-to-female ratio of 1.2:1. The ECOG of MM patients were ECOG 0–1 (37.7%) and ECOG ≥2 (62.3%). Furthermore, anemia was present among 47.7% of MM patients. The serum albumin was low among 40.8% of MM patients, while serum creatinine and LDH were high in 20% and 68.5% of MM patients, respectively. The prevalence of hypercalcemia among MM patients after calcium correction was 17.7% [Table 1].

Durie-Salmon staging of MM patients showed commonly Stage II (53.8%). ISS staging of MM patients revealed predominantly Stage II (47.7%). Of the MM patients, 79.2% of them were alive and 20.8% were dead [Table 2].

No significant differences were observed between MM patients with or without hypercalcemia regarding age of the patients (*P* = 0.43), gender (*P* = 0.81), and ECOG (*P* = 0.14). Furthermore, no significant differences were observed between MM patients with or without hypercalcemia regarding anemia (*P* = 0.98), serum albumin (*P* = 0.77), and LDH (*P* = 0.29). Serum creatinine level is significantly high among MM patients with hypercalcemia (*P* = 0.01) [Table 3].

A significant association was observed between advanced Durie-Salmon stages of MM patients and hypercalcemia (*P* = 0.01). No significant differences were observed between MM patients with or without hypercalcemia regarding ISS staging (*P* = 0.213). There was a significant association between high death rates and MM patients with hypercalcemia (*P* = 0.01) [Table 4].

As shown in Figure 1, the mean survival of MM patients was 4.5 years (95% confidence interval [CI] 3.9–5.1 years). The 3-year survival among cases was 72%, while the 6-year survival was 41%.

**Table 1: Demographic, clinical and laboratory characteristics of multiple myeloma patients**

Variable	n (%)
Age (years)	
<60	66 (50.7)
≥60	64 (49.3)
Gender	
Male	70 (53.8)
Female	60 (46.2)
ECOG	
0–1	49 (37.7)
≥2	81 (62.3)
Anemia	
No	68 (52.3)
Yes	62 (47.7)
Serum albumin	
>3.5	77 (59.2)
<3.5	53 (40.8)
Serum creatinine	
<2	104 (80.0)
≥2	26 (20.0)
LDH	
Normal	41 (31.5)
High	89 (68.5)
Corrected calcium	
No hypercalcemia	107 (82.3)
Hypercalcemia	23 (17.7)
Total	130 (100.0)

ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase

**Table 2: Staging and outcome of multiple myeloma patients**

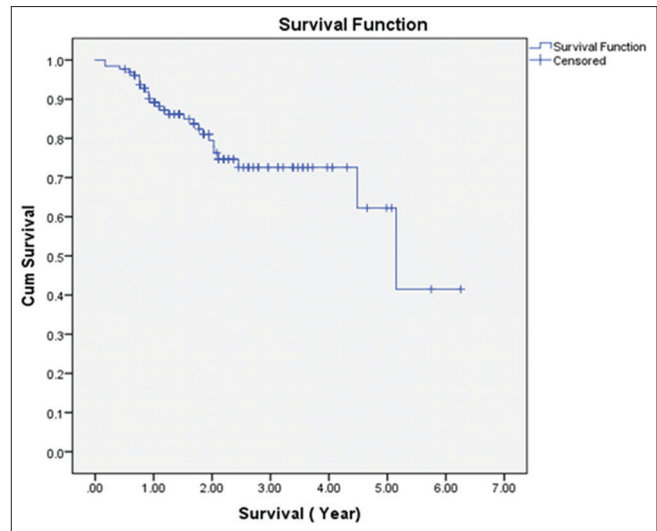
Variable	n (%)
Stage of disease (Durie-Salmon)	
I	17 (13.1)
II	70 (53.8)
III	43 (33.1)
Stage of disease (ISS)	
I	35 (26.9)
II	62 (47.7)
III	33 (25.4)
Current patient status	
Alive	103 (79.2)
Dead	27 (20.8)
Total	130 (100.0)

ISS: International Staging System

The 3-year survival among hypercalcemic cases was 61% while among nonhypercalcemic cases was 75%. The 6-year survival of nonhypercalcemic patients was 42% [Figure 2].

## DISCUSSION

The hypercalcemia is represented as the most interesting complication of MM with unclear pathogenesis till now.<sup>[8]</sup> The



**Figure 1:** Kaplan–Meier curve for survival of multiple myeloma patients, X = Cumulative survival in %, Y = Duration of follow-up in years

current study showed a frequency of 17.7% for hypercalcemia among MM patients. This finding is lower than results of Kastritis *et al.*'s<sup>[13]</sup> study in Greece which found that 21% of patients with MM had hypercalcemia by reviewing data of newly diagnosed MM cases reported by Greek Myeloma Study Group. However, our study's frequency is higher than the results of Kyle *et al.*'s<sup>[14]</sup> study in the USA which revealed that 13% of patients with MM had hypercalcemia. In general, the hypercalcemia related to malignancy was found to be prevalent in about 20% of all cancer patients during their clinical course, and the most common malignancies related to hypercalcemia is MM with highest prevalence of hypercalcemia reaching to range of 15%–20%.<sup>[15]</sup> In the UK, the first systematic analysis population-based study carried out by Jick *et al.*<sup>[16]</sup> reported that the hypercalcemia prevalence increased in general among cancer patients, but higher increase was obvious among patients with lung cancer, MM, and Stage IV of cancers.

In the present study, the serum creatinine level was significantly higher among MM patients with hypercalcemia ( $P = 0.01$ ). Similarly, Eleutherakis-Papaiaikovou *et al.*'s<sup>[17]</sup> study in Greek found that hypercalcemia in MM patients is considered as high prevalent with renal insufficiency.

The current study showed a significant association between advanced Durie-Salmon stages of MM patients and hypercalcemia ( $P = 0.01$ ). This finding agrees with the reports of many literature regarding as hypercalcemia one of elements of Durie-Salmon staging of MM.<sup>[18,19]</sup> In our study, MM patients with hypercalcemia had a significantly higher mortality rate (39.1%) than MM patients with no hypercalcemia (16.8%). Consistently, a retrospective review study carried out in Spain by Lakhwani *et al.*<sup>[20]</sup> found that hypercalcemia increased aggressiveness and death rates of MM. Many authors found that hypercalcemia accompanying malignancy is related to severe clinical signs and symptoms and is often an oncologic emergency.<sup>[21,22]</sup>

The mean survival of MM patients in our study was 4.5 years and the 3-year survival was 72% that declined to 41% for 6-year survival. These survival rates of MM patients are better than the survival of MM patients in Baghdad as reported by Alwan's study in Iraq which reported a mean survival of 2.9 years.<sup>[23]</sup> However, these findings are lower than the results of Hameed *et al.*'s<sup>[24]</sup> study in Pakistan which found that 85% of MM patients had 3-year survival rate with 4-year overall survival. These differences might be attributed to advances in supportive care with increasing in number of new novel

agents each year, with possible differences in genetic and ethnic background of each patient population.

Our study showed a shorter survival of MM patients with hypercalcemia than the survival of patients without hypercalcemia. This finding coincides with results of Zagouri *et al.*'s<sup>[12]</sup> study in Greece which found that hypercalcemia remains as a poor prognostic characteristic of MM despite the introduction of novel therapies. In addition, Yusuf *et al.*'s<sup>[25]</sup> study in the USA reported that increased age, male gender, previous comorbidities, anemia, and hypercalcemia are common risk factors for early death of newly diagnosed MM patients.

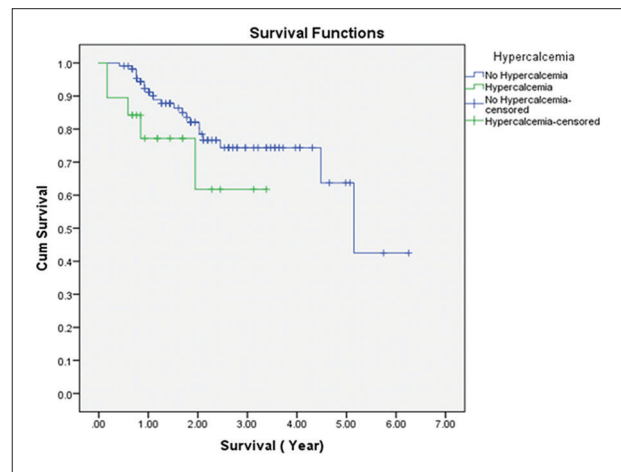
**Table 3: Distribution of patients' demographic, clinical and laboratory characteristics**

Variable	Corrected calcium		P
	No hypercalcemia, n (%)	Hypercalcemia, n (%)	
Age (years)			
<50	56 (52.3)	10 (43.5)	0.43
≥60	51 (47.7)	13 (56.5)	
Gender			
Male	57 (53.3)	13 (56.5)	0.81
Female	50 (46.7)	10 (43.5)	
ECOG			
0-1	45 (42.1)	4 (17.3)	0.14
≥2	62 (57.9)	19 (82.6)	
Anemia			
No	56 (52.3)	12 (52.2)	0.98
Yes	51 (47.7)	11 (47.8)	
Serum albumin			
>3.5	64 (59.8)	13 (56.5)	0.77
<3.5	43 (40.2)	10 (43.5)	
Serum creatinine			
<2	90 (84.1)	14 (60.9)	0.01
≥2	17 (15.9)	9 (39.1)	
LDH			
Normal	37 (34.6)	4 (17.4)	0.29
High	70 (65.4)	19 (82.6)	

ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase

## CONCLUSIONS

The frequency of hypercalcemia among MM patients in KRI is within international acceptable range. The hypercalcemia accompanying MM is regarded as a poor prognostic factor that is associated with higher mortality and shorter survival. Implementing strict guidelines in the treatment of hypercalcemia for patients with MM is essential for improving prognosis.



**Figure 2:** Kaplan–Meier curve for survival of multiple myeloma patients according to hypercalcemia prevalence

**Table 4: Distribution of patients' general characteristics according to hypercalcemia**

Variable	Corrected calcium		P
	No hypercalcemia, n (%)	Hypercalcemia, n (%)	
Stage of disease			
I	17 (15.9)	0	0.01
II	60 (56.1)	10 (43.5)	
III	30 (28.0)	13 (56.5)	
Stage of disease (ISS)			
I	32 (29.9)	3 (13.0)	0.213
II	50 (46.7)	12 (52.2)	
III	25 (23.4)	8 (34.8)	
Current patient status			
Alive	89 (83.2)	14 (60.9)	0.01
Dead	18 (16.8)	9 (39.1)	

ISS: International Staging System

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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