E-ISSN 2250-0944
ISSN 2250-1150
DOI: 10.48047/ijprt/16.01.173

Research Article

Association of Hypercalcemia with Disease Severity in Plasma Cell Dyscrasias

Rafiq Ahmed Shahid[1], Attia Lateef[2], Hussain Farooq[3], Usman Nasir[4], Aafrinish Amanat[5], Madiha Ehsan-ul-Haq[6]

[1,4-6]Associate Professors, Department of Pathology, Sharif Medical & Dental College, Lahore, Pakistan
[2]Assistant Professor, Department of Pathology, Sharif Medical & Dental College, Lahore, Pakistan
[3]Assistant Professor, Department of Hematology, Shaikh Zayed Postgraduate Medical Institute, Lahore, Pakistan

Corresponding Author: Dr. Usman Nasir, Associate Professor, Department of Pathology, Sharif Medical & Dental College, Lahore, Pakistan. E-mail: docusman196@gmail.com

Received: 20.12.25 | Revised: 19.02.26 | Accepted: 27.02.26 | Published: 12.03.2026

ABSTRACT

Background: Plasma cell dyscrasias are characterized by clonal plasma cell proliferation and multisystem involvement.

Objective: To assess the association between hypercalcemia and disease severity in patients with plasma cell dyscrasias.

Methodology: This was a descriptive, cross-sectional study conducted at Department of Pathology, Sharif Medical & Dental College Lahore Pakistan from 1st January 2025 to 30th June 2025 including 55 patients diagnosed with plasma cell dyscrasias. Patients presenting to hematology outpatient and inpatient services were assessed systematically at the time of diagnosis or during active disease evaluation.

Results: The mean corrected serum calcium level was 11.2±1.7 mg/dL, and hypercalcemia was observed in 50.9% of patients. Patients with hypercalcemia had significantly lower hemoglobin levels (8.3±1.6 g/dL vs. 9.9±1.7 g/dL), higher serum creatinine levels (3.1±1.5 mg/dL vs. 1.5±0.7 mg/dL), and lower estimated glomerular filtration rates (31.4±14.6 mL/min/1.73m^2 vs. 54.2±16.8 mL/min/1.73m^2) compared to normocalcemic patients. Extensive bone disease was more frequent in hypercalcemic patients, with 64.3% having three or more lytic lesions. Advanced disease stage was observed in 67.9% of hypercalcemic patients versus 18.5% of normocalcemic patients. Corrected serum calcium showed significant correlations with hemoglobin ($r = -0.51$), serum creatinine ($r = 0.58$), estimated glomerular filtration rate ($r = -0.55$), and disease stage ($r = 0.60$).

Conclusion: It is concluded that hypercalcemia is strongly associated with increased disease severity in plasma cell dyscrasias. Elevated serum calcium levels correlate with worsening hematological, renal, and skeletal involvement and advanced disease stage, underscoring the importance of routine calcium assessment for early identification of high-risk patients and optimized disease management.

Keywords: Plasma cell dyscrasias, Hypercalcemia, Disease severity, Multiple myeloma

INTRODUCTION

Plasma cell dyscrasias are a heterogeneous group of hematological disorders that are characterized by clonal expansion of the plasma cells and excess of monoclonal immunoglobulins or light chains.[1] Some of these disorders are the asymptomatic monoclonal gammopathy of undetermined significance to malignancies that are vicious like the multiple myeloma.[2] Among them, the most clinical important one is multiple myeloma since it has systemic complications and progressive nature. The severity of the diseases in plasma cell dyscrasias is a combination of tumor burden, organ involvement and metabolic abnormalities.[3] The most common clinical outcomes include anemia, renal failure, bone defects, frequent infections, and metabolic imbalance, which are all the features of the disease and its outcomes.[4]

Only when the markers of the severity of the disease are found, it is possible to conduct risk stratification and early corrective treatment. Hypercalcemia is one of the most frequent and clinically relevant metabolic complications reported in the plasma cell dyscrasia particularly in multiple myeloma.[5] It is predominantly brought about by hyperplasia in the osteoclastic bone resorption of malignant plasma cells through discharge of osteoclast-activating factors and cytokines such as interleukins and receptor activating nuclear factor-k ligand.[6,7] The inhibition of the osteoblastic proliferation also leads to the erosion of the calcium in the bone worsening hypercalciemia.[8]

Hypercalcemia is a condition that is usually linked to later disease and widespread skeletal involvement. High serum calcium levels can result

in severe clinical effects, such as dehydration, renal failure, neurocognitive disorders, cardiac arrhythmias, as well as gastrointestinal complications that can cause enhanced morbidity and mortality.[9,10] Consequently, hypercalcemia is a medical emergency among patients with plasma cell dyscrasias and it is frequently urgent. A number of disease severity evaluation systems use hypercalcemia as one of the characteristic features. CRAB symptoms are commonly used to diagnose symptomatic disease in need of treatment using the classical CRAB criteria; hypercalcemia, renal impairment, anemia, and bone lesions.[11]

Hypercalcemia in the context is also seen as an indication of active disease and tumor burden thus highlighting its clinical significance in terms of disease staging and prognosis.[12] Hypercalcemic patients are more likely to have an advanced disease, an increased plasma cell infiltration, and worsened kidney functioning and overall outcomes than normocalcemic patients.[13] The extent to which hypercalcemia is associated with certain parameters of severity, including anemia, renal impairment and skeletal involvement, is, however, variably reported in other populations. Although its significance is acknowledged, scant evidence exists in studies focusing specifically on the relationship between hypercalcemia and the signs of disease severity in patients with plasma cell dyscrasias, especially in resource-constrained environments. Having a better comprehension of this correlation could assist clinicians in recognizing the high-risk patients more efficiently and improve the management strategies.[14]

MATERIALS AND METHODS

This was a descriptive, cross-sectional study conducted at Department of Pathology, Sharif Medical & Dental College Lahore Pakistan from 1st January 2025 to 30th June 2025 including 55 patients diagnosed with plasma cell dyscrasias. All patients of either gender aged 18 years and above, diagnosed cases of plasma cell dyscrasias, including multiple myeloma and related disorders, availability of complete clinical, biochemical, and radiological data and willing to provide informed consent were included. The patients having hypercalcemia due to causes other than plasma cell dyscrasias, known primary hyperparathyroidism, chronic kidney disease unrelated to plasma cell dyscrasia, recent use of calcium or vitamin D supplementation, incomplete laboratory or staging data and unwilling to participate were excluded. The demographic data, clinical presentation, hemoglobin levels, parameters of renal functions, serum calcium levels, and degree of bone involvement were recorded. The level of serum calcium was measured and adjusted according to serum albumin level based on standard correction formulas. Hypercalcemia was categorized based on the set lab reference ranges. The severity of the disease was determined by using clinical and laboratory signs that were identified, such as anemia and renal impairment, skeletal involvement, and disease staging criteria. Standard laboratory procedures were used in the institutional laboratory to conduct all laboratory investigations as a way of ensuring consistency and accuracy. The SPSS version 24.0 was used in data analysis. Chi-square and independent t-tests were used to provide association between hypercalcemia and parameters of disease severity. The severity of disease indicators as continuous variables was evaluated through correlation analysis with levels of serum calcium. The p-value of <0.05 was assumed to be statistically significant

RESULTS

The mean age was 58.4±10.6 years, ranging from 34 to 78 years, indicating predominance of older adults. There were 33 (60%) males and 22 (40%) females. The mean duration of symptoms before presentation was 6.8±3.4 months, reflecting delayed diagnosis. Multiple myeloma was the dominant diagnosis, present in 46 (83.6%) of patients. Bone pain was the most common symptom in 41 (74.5%), while pathological fractures were observed in 17 (30.9%), suggesting advanced skeletal disease. Weight loss was noted in 29 (52.7%) and recurrent infections in 21 (38.2%) indicating significant systemic involvement (Table 1).

Biochemical analysis revealed a mean total serum calcium level was 10.9±1.6 mg/dL and a mean corrected calcium level was 11.2±1.7 mg/dL, both exceeding normal reference limits. Hypercalcemia was present in 28 (50.9%) of patients after albumin correction. Mean serum albumin was 3.4±0.5 g/dL, indicating mild hypoalbuminemia in a substantial proportion of patients. Mean serum phosphorus was 4.8±1.2 mg/dL while serum LDH levels were elevated with a mean value was 389±112 U/L, reflecting increased cellular turnover and disease activity (Table 2).

Mean hemoglobin level was 9.1±1.8 g/dL with 61.8% (n=34) of patients having hemoglobin levels below 10 g/dL, indicating significant anemia. Mean serum creatinine was 2.3±1.4 mg/dL, and 52.7% (n=29) had creatinine levels ≥2 mg/dL. Renal function was further compromised, with a mean eGFR of 42.6±18.9 mL/min/1.73m2, and 67.3% (n=37) having eGFR values below 60 mL/min/1.73m2. Bone lesions were detected in 69.1% (n=38) of patients, while 38.2% (n=21) had three or more lytic lesions. Advanced disease stage was common, with 43.6% (n=24) classified as ISS stage III. Mean β2-microglobulin level was 6.2±2.1 mg/L, with nearly half of patients exceeding the high-risk threshold (Table 3).

Mean corrected calcium was 12.6±1.3 mg/dL in the hypercalcemia group versus 9.7±0.4 mg/dL in the normocalcemia group. Hypercalcemic patients had lower mean hemoglobin levels (8.3±1.6 g/dL) compared to normocalcemic patients (9.9±1.7 g/dL). Renal impairment was more pronounced, with mean serum creatinine of 3.1±1.5 mg/dL versus 1.5±0.7 mg/dL, and mean eGFR of 31.4±14.6 mL/min/1.73m2 compared to 54.2±16.8 mL/min/1.73m2. Extensive bone disease was present in 64.3% (n=18) of hypercalcemic patients versus 11.1% (n=3) of normocalcemic patients. ISS stage III disease was observed in 67.9% (n=19) of hypercalcemic patients compared to 18.5% (n=5) of normocalcemic patients (Table 4).

Renal impairment was present in 78.6% (n=22) of hypercalcemic patients compared to 33.3% (n=9) of normocalcemic patients. Anemia was observed in 85.7% (n=24) versus 55.6% (n=15), while bone disease was present in 89.3% (n=25) versus 48.1% (n=13). Two or more CRAB features were identified in 75.0% (n=21) of hypercalcemic patients compared to 25.9% (n=7) of normocalcemic patients. All CRAB features were present simultaneously in 50.0% (n=14) of hypercalcemic patients versus 11.1% (n=3) of normocalcemic patients, highlighting severe multisystem involvement (Table 5).

Corrected calcium showed a moderate negative correlation with hemoglobin ($r = -0.51$), indicating worsening anemia with rising calcium levels. A strong positive correlation was observed with serum creatinine ($r = 0.58$), and a negative correlation with eGFR ($r = -0.55$), confirming progressive renal dysfunction. Calcium levels were positively correlated with the number of bone lesions ($r = 0.47$) and disease stage ($r = 0.60$). Regression analysis showed that increasing calcium levels were associated with a 0.42 g/dL decrease in hemoglobin, a 0.71 mg/dL rise in creatinine, and a 4.9 mL/min/1.73m2 decline in eGFR (Table 6).

Table 1: Expanded baseline demographic and clinical characteristics of patients (n = 55)

Variable	No.	%
Gender		
Male	33	60.0
Female	22	40.0
Age (years)	58.4±10.6	
Duration of symptoms (months)	6.8±3.4	
Multiple myeloma	46	83.6
Other plasma cell dyscrasias	9	16.4
Bone pain	41	74.5
Pathological fractures	17	30.9
Weight loss	29	52.7
Recurrent infections	21	38.2

Table 2: Detailed serum calcium and biochemical profile (n = 55)

Parameter	Mean±SD	Median	Minimum	Maximum	Abnormal
Total serum calcium (mg/dL)	10.9±1.6	10.7	8.6	14.8	26 (47.3%)
Corrected calcium (mg/dL)	11.2±1.7	11.0	8.9	15.1	28 (50.9%)
Serum albumin (g/dL)	3.4±0.5	3.4	2.3	4.5	31 (56.4%)
Serum phosphorus (mg/dL)	4.8±1.2	4.7	2.6	7.2	24 (43.6%)
Serum LDH (U/L)	389±112	372	210	678	33 (60.0%)
Hypercalcemia status	28 (50.9%)	1	1	1	Biochemical abnormality present

Table 3: Expanded disease severity parameters (n = 55)

Parameter	Mean±SD	Median	Minimum	Maximum	Severity
Hemoglobin (g/dL)	9.1±1.8	9.0	5.6	13.2	<10 g/dL: 34 (61.8%)
Serum creatinine (mg/dL)	2.3±1.4	2.0	0.8	6.5	≥2 mg/dL: 29 (52.7%)
eGFR (mL/min/1.73m²)	42.6±18.9	41	9	88	<60: 37 (67.3%)
Bone lesions on imaging	38 (69.1%)	1	1	1	Radiological involvement
≥3 lytic bone lesions	21 (38.2%)	1	1	1	Extensive skeletal disease
ISS stage III	24 (43.6%)	1	1	1	Advanced disease stage
β2-microglobulin (mg/L)	6.2±2.1	6.0	2.8	11.4	>5.5: 26 (47.3%)

Table 4: Comparison of disease severity by calcium status

Parameter	Hypercalcemia (n=28)	Normocalcemia (n=27)	Mean Difference	Effect Size (Cohen's d)	p-value
Corrected calcium (mg/dL)	12.6±1.3	9.7±0.4	2.9	2.80	<0.001
Hemoglobin (g/dL)	8.3±1.6	9.9±1.7	1.6	0.96	0.001
Serum creatinine (mg/dL)	3.1±1.5	1.5±0.7	1.6	1.40	<0.001
eGFR (mL/min/1.73m²)	31.4±14.6	54.2±16.8	22.8	1.45	<0.001
≥3 bone lesions	18 (64.3%)	3 (11.1%)	53.2%	1.75	<0.001
ISS stage III	19 (67.9%)	5 (18.5%)	49.4%	1.62	<0.001

Table 5: Distribution of CRAB features by calcium status

CRAB Feature	Hypercalcemia	Normocalcemia	Relative Risk	p-value
Hypercalcemia	28 (100%)	-	3.00	<0.001
Renal impairment	22 (78.6%)	9 (33.3%)	2.36	<0.001
Anemia	24 (85.7%)	15 (55.6%)	1.54	0.01
Bone disease	25 (89.3%)	13 (48.1%)	1.86	0.002
≥2 CRAB features	21 (75%)	7 (25.9%)	2.89	<0.001
All CRAB features	14 (50%)	3 (11.1%)	4.50	0.003

Table 6: Correlation and regression analysis between corrected calcium and disease severity

Parameter	Pearson r	R^2	Regression β	SE β	95% CI Lower	95% CI Upper	p-value
Hemoglobin (g/dL)	−0.51	0.26	−0.42	0.10	−0.62	−0.22	<0.001
Serum creatinine (mg/dL)	0.58	0.34	0.71	0.14	0.44	0.98	<0.001
eGFR (mL/min/1.73m²)	−0.55	0.30	−4.9	0.9	−6.8	−3.0	<0.001
Number of bone lesions	0.47	0.22	0.63	0.14	0.34	0.92	0.001
ISS stage (I–III)	0.60	0.36	0.78	0.13	0.52	1.04	<0.001

DISCUSSION

Almost half of the population in this study had hypercalcemia and such patients demonstrated much worse hematological, renal, skeletal involvement suggesting that hypercalcemia is a strong predictor of disease burden and not a single biochemical abnormality. The average of the corrected serum calcium level of the patients in the current study was 11.2+.7 mg/dL, and hypercalcemia was observed in 50.9% of the cases. The previous researches have demonstrated similar prevalence rates of hypercalcemia in plasma cell dyscrasias with high tumor burden and bone destruction being frequently linked with high levels of calcium in plasma.[15,16] The frequency of hypercalcemia in this cohort is high and indicates high level of skeletal involvement and hyperactive disease biology. A significant observation was anemia with mean hemoglobin of 9.1er 1.8 g/dL, and close to two-thirds of the patients with hemoglobin value of less than 10 g/dL. The level of hemoglobin was found to be significantly low in hypercalcemic patients than in normocalcemic patients indicating more severe marrow infiltration. The same has been demonstrated previously indicating that hypercalcemia is usually accompanied by serious anemia confirming its association with advanced marrow disease and increased plasma cell infiltration.[17,18]

Hypercalcemic patients had a significant higher prevalence of renal dysfunction. The mean serum creatinine was also found to be high and the mean eGFR was also low in the patients who had high calcium levels, thus had evident renal impairment. Past studies have consistently indicated that hypercalcemia also helps to cause renal damage via dehydration, nephrocalcinosis and light chain mediated lesions, which supports the close relationship between calcium imbalance and kidney injury as witnessed in this research.[19]

Hypercalcemic patients had a much worse skeletal engagement wherein a greater proportion of patients had multiple lytic bone lesions and pathological fractures. Hypercalcemic patients also had a high percentage of extensive lytic disease that was almost two-thirds of the patients, whereas a small percentage of normocalcemic patients had extensive lytic disease. Close correlations between hypercalcemia and severe bone disease were observed in prior studies where high levels of calcium were strongly connected with high activity in osteoclastic activity and inhibited bone formation.[20]

The disease stage also emphasized the correlation between hypercalcemia and a serious disease. The

relatively greater percentage of hypercalcemic patients was in stage III in comparison to normocalcemic patients. It has been previously demonstrated that hypercalcemia is very common in later stages of the plasma cell dyscrasia and it is related to worse prognosis and worse survival outcomes, which confirms the staging trend we observed in the present study.[21] The quantitative relationship between the serum calcium levels and the severity of the disease was confirmed further through correlation and regression analysis. The upsurge of calcium was linked with deepening of anemia, progressive kidney dysfunction, augmented skeletal engagement, and the elevation of disease phase. Similar patterns of correlation between calcium and disease aggressiveness have been previously reported that support the biological feasibility of calcium as a disease surrogate marker.

CONCLUSION

Hypercalcemia is significantly associated with increased disease severity in patients with plasma cell dyscrasias. Patients with elevated serum calcium levels exhibited more severe anemia, greater renal impairment, extensive skeletal involvement, and advanced disease stage compared to normocalcemic patients. The strong correlation between corrected calcium levels and multiple severity indicators highlights hypercalcemia as a reliable marker of aggressive disease and high tumor burden. Routine assessment and early management of hypercalcemia may aid in timely identification of high-risk patients and guide more intensive therapeutic strategies to improve clinical outcomes.

REFERENCES

1. El Maachi N, Haidouri S, Benlachgar N, Aziza B, Tazi Mezalek Z. The rarest subtype of plasma cell dyscrasia: IgE multiple myeloma. *Cureus* 2025; 17(9): e91401.
2. Corsale AM. Prediction of progression to symptomatic multiple myeloma in patients with high-risk plasma cell dyscrasias. *Universita degli Studi di Palmero* 2025.
3. Kavvathas S, Toor J, Maknouni B, Allazeh A, Hasan M. A case of rare pulmonary manifestations in multiple myeloma. *Am J Respir Crit Care Med* 2025; 211: A7007-9.
4. Morgan HT, Derman BA, Ma H, Kumar SK. Changing lanes: extending CAR T-cell therapy to high-risk plasma cell dyscrasias. *Frontiers in Immunology* 2025; 16: 1558275.
5. Gupta A, Devi A, Narwal A, Kamboj M. Unveiling the mysterious plasma cell lesions of oral cavity: a 13-year institutional experience. *J Maxillofac Oral Surg* 2025; 1-9.
6. Kumar S, Ahmed F, Mundada M, Kondandapani S, Kumar P. Surprising visit: the rare plasma cell variant. *Blood Science* 2025; 7(1): e00218.
7. Cherukuri S, Li L, Soff S, Andrzejczyk A, Ahmed T. Relapsing IgD myeloma with increased circulating plasma cells: clinical case report and literature review. *J Assoc Genet Technol* 2025; 51(1): 21-24.
8. Goel R, Liu J, Jordak K, Malik M. Lambda light chain multiple myeloma in a 47-year-old female patient on long-term clozapine therapy. *Cureus* 2025; 17(9): e92079.
9. Pezzuto F, Fiorentù G, Castelli G, Zanella S, Giraudo C, Tinè M, Calabrese F. Pulmonary plasma cell disorders: histopathology, diagnosis, and clinical perspectives. *Virchows Archiv* 2025; 487(3): 573-86.
10. Ugwu C, Onyenemezu K, Okere U, Taneja A. MM-872: racial disparities in clinical outcomes among patients with newly diagnosed multiple myeloma in the United States: A 21-year comparative analysis. *Clin Lymphoma Myeloma Leukemia* 2025; 25: S944-5.
11. Koo E, Albert S, Patrick B, Rhiwi Y, Henia M, Visram A. Prior plasma cell dyscrasia is associated with lower odds of severe myeloma-defining events at diagnosis. *Clin Lymphoma Myeloma Leukemia* 2025; 25: S257.
12. Wang X, An N, Hu J, Gao Y, Yu Q, Bao Y, Li C. Efficacy and safety of daratumumab-based regimens in light chain amyloidosis: a retrospective single-center study. *Clin Lymphoma Myeloma Leukemia* 2025; 25: S257-8.
13. Madyalkar S, Mahesh E, Gurudev KC, Gireesh M, Reddy R, Reddy H, Prabhu P. WCN25-2384 a study of hypomagnesemia on clinical outcome of critically ill patients in medical intensive care unit in a tertiary care centre. *Kidney International Reports* 2025; 10(2): S5.
14. Bakan A, Ceylan HZ, Durusoy AF, Ercan S. Sarcoidosis case with acute renal failure, nephrolithiasis, and hypercalcaemia after uncontrolled D3 vitamin supplementation. *EMJ Nephrology* 2025; 13(1): 64-72.
15. Waqar A, Bin SM, Asghari H, Blue B. Plasma cell disorders. *Handbook of Hematology Malignancies* 2025: 275.
16. Mahto M, Kumar A, Rai N, Kumar V, Kumar S, Kumar T. The missing M band: Is it really non-secretory multiple myeloma? *EJIFCC* 2025; 36(1): 74.
17. Ravi S, Sundaresan D, Pai S, Kalashetty M. MPL-mutated primary myelofibrosis and multiple myeloma–a rare coexistence. *Indian J Hematol Blood Transfusion* 2025; 1-4.
18. Hanbali A, Alamer A, Alhayli S. Uncommon entities, uncommon challenges: a review of rare plasma cell disorders. *Hematology Reports* 2025; 17(4): 31.

19. Jaccard A, Pascal V, Magy L, Roussel M. POEMS Syndrome. *La Presse Médicale* 2025; 54(1): 104270.
20. Hanamura I, Karnan S, Ota A, Takami A. Primary plasma cell leukemia: recent advances in molecular understanding and treatment approaches. *Int J Molecular Sciences* 2025; 26(13): 6166.
21. Sutanto H, Romadhon PZ, Fatmawati VR, Waitupu A, Ansharullah BA. Multiple myeloma and precursor plasma cell disorders: from emerging driver mutations to current and future therapeutic strategies. *Hematology* 2025; 6(3): 29.