**Outcomes of hypercalcemia in patients with Multiple Myeloma: A Population-Based Study Using National Inpatient Sample (NIS) Database**

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**Abstract:**

**Background:**

Multiple myeloma (MM) has different complications, including renal failure, anemia, infections, metabolic complications, and skeletal problems. Hypercalcemia is the most common metabolic complication, and the presence of hypercalcemia indicates worse outcomes.

**Aims:**

The study aims to examine outcomes such as hospitalization costs, length of stay, survival rates, and the incidence of complications of hypercalcemia in multiple myeloma patients admitted in the United States from 2017 to 2020.

**Methods:**

We performed a retrospective analysis using the National Inpatient Sample database to determine the incidence of hypercalcemia in patients admitted to United States hospitals from 2017 to 2020. Univariate and multivariate logistic regression were used to calculate the odds ratio. We used STATA software 17 to perform the analysis.

**Results:**

We found that the total number of patients with MM was 437799, out of which 8.6% had hypercalcemia. The mean age of the patients was 69 years, and hypercalcemia was found to be more common in males (55%) than females (45%). The presence of hypercalcemia was also associated with increased mortality (adjusted odds ratio 1.3, p-value 0.00). It was also seen that MM patients who had hypercalcemia had a higher risk of complications, including acute kidney injury (OR 3, p<0.05), hyperkalemia (OR 1.8, p-value <0.05), metabolic acidosis (1.4, p-value <0.05), spinal cord compression (OR 0.9, p-value >0.05), increased length of stay (OR 3, p-value <0.05), and higher cost of hospitalizations (p-value <0.05).

**Conclusion:**

The data is also limited to the demographic characteristics, impact, and outcomes of hypercalcemia on patients with MM. This study contributes valuable insights into the clinical implications of hypercalcemia in patients with multiple myeloma (MM). It fills existing gaps in the literature by utilizing a large population-based dataset.

**Key Words:**

Multiple Myeloma, Hypercalcemia, Metabolic complications, National Inpatient Sample

**Introduction**:

The overproduction of a clonal plasma cell population characterizes multiple myeloma (MM). This malignancy accounts for 1-2% of the cancer-related deaths that occur in the US (1). It has various features, such as renal failure, anemia, infections, and skeletal problems. The most common metabolic complication that occurs in MM is hypercalcemia. It is higher in patients with a higher tumor burden (1). The exact mechanism of Hypercalcemia in MM is not precise. Recently, new evidence has suggested that hypercalcemia is thought to be caused by increased osteoclast-mediated bone resorption, driven by several factors secreted by the clonal plasma cell population, including inflammatory cytokines and the receptor activator of nuclear factor K-B ligand (RANK-L) (2). Its prognostic value in MM at large is not clearly defined, although when present in newly diagnosed MM (NDMM), it correlates with increased mortality (3).

In the present study, we set out to better characterize hypercalcemia's role during MM hospitalization, the demographics of the patients, and its impact on outcomes and mortality.

**Material and Methods:**

**Data Source:**

This study is a retrospective analysis that was conducted using a national inpatient sample database (NIS). This database is updated annually regarding the discharge across the US hospitals and contains information about almost 7–8 million hospital stays at approximately 1000 random hospitals [1]. It also includes data regarding patient demographics, comorbidities, length of stay, hospital charges, and payment sources. Codes used in this are the ​​International Classification of Diseases, Tenth Edition, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS, and are used to make primary and secondary diagnoses.

**Study Population:**

We used the NIS database from 2017 to 2020 to identify patients over> 18 with a primary diagnosis of multiple myeloma. The study population was divided into two groups, those with hypercalcemia and those without hypercalcemia, using the ICD-10 code. We looked at the two groups' all-cause mortality, length of stay, hospital charges, and complications.

**Statistical Analysis:**

We used the STATA® Version 17.0 software to analyze the data. An initial analysis was conducted to see the difference in outcomes, complications, length of stay, and hospitalization costs among patient cohorts. We used the student t-test for continuous variables, while chi-square was used for categorical variables. Univariate logistic regression was used to calculate the unadjusted Odds ratio. To account for possible confounders, we used multivariate logistic regression. A P-value of <0.05 was considered statistically significant for all the tests.

**Results**:

**The proportion of patients with hypercalcemia:**

We found that a total of 437799 patients with multiple myeloma were admitted to hospitals in the United States from the year 2017 to 2020. Out of them, 8.6% of the patients were found to have hypercalcemia during admission (37,765 patients).

**Baseline Demographics:**

The patients were divided into categories based on gender, race, mean household income, insurance, and hospital bed size. Demographics of the patients admitted with multiple myeloma who had hypercalcemia compared to those who did not have hypercalcemia have been shown in the table (Table 1). The mean age of the patients who had hypercalcemia was around 69 years. Hypercalcemia in multiple myeloma was more common in Males ( 55%, p-value 0.00) than in females (45%, p-value 0.00) (figure 1).

The details of other characteristics of the patients have been shown in the table 1.

The incidence was highest in white race (60%), and lowest in Native Americans (1%, p-value 0.00). The incidence was also highest in large-volume hospitals compared to low-volume hospitals with fewer beds ( 54% vs 18%) (figure 2).

**Figure 1 illustrates the occurrence of hypercalcemia in male and female patients with multiple myeloma (MM)**

**Figure 2 depicts the prevalence of hypercalcemia among different racial groups with multiple Myeloma (MM)**

**Table 1 showing the demographic characteristics of the patients with multiple myeloma (MM)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Demographics** | **With Hypercalcemia** | **Without Hypercalcemia** | **P- value** |
| **Gender (%)** |  |  |  |
| Female | 45 | 56 | 0.00 |
| Male | 55 | 44 | 0.00 |
| **Race (%)** |  |  |  |
| White | 60 | 64 | 0.00 |
| Black | 25 | 22 | 0.00 |
| Hispanic | 9 | 8 | 0.00 |
| Asian | 2 | 2 | 0.00 |
| Native American | 1 | 1 |  |
| Other | 3 | 3 |  |
| **Median Household Income (%)** |  |  |  |
| 0-25th percentile | 30 | 27 | 0.00 |
| 26th to 50th percentile (median) | 24 | 25 | 0.00 |
| 51st to 75th percentile | 24 | 24 | 0.00 |
| 76th to 100th | 22 | 24 | 0.00 |
| **Bed Size of the hospital (%)** |  |  |  |
| Small | 18 | 18 | 0.00 |
| Medium | 28 | 26 | 0.00 |
| Large | 54 | 56 | 0.00 |

**Complications and outcomes:**

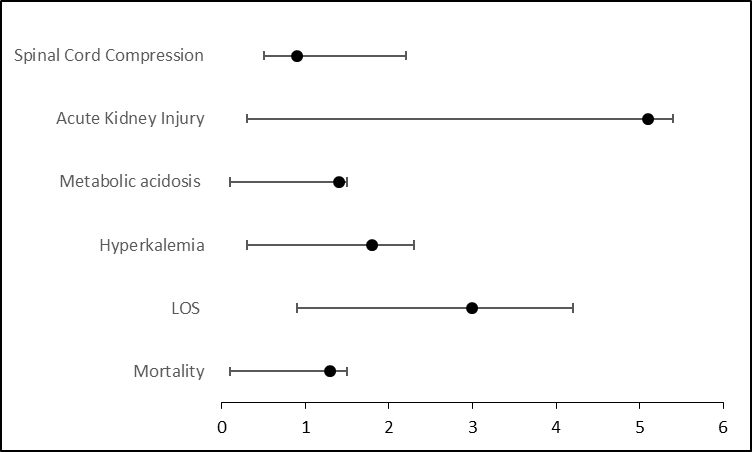
The presence of hypercalcemia increased the mortality of patients with multiple myeloma ( 2354 patients died out of a total of 37765 who had hypercalcemia) ( OR 1.3, p-value 0.00). Compared to the patients who did not have hypercalcemia, the elevated calcium in the patients increased the odds of hyperkalemia ( n= 565 patients, 1.4%) ( p-value 0.00) ), metabolic acidosis (n= 6540 patients, 17%) (p-value 0.00) and acute kidney injury ( n= 25414 patients, 67%) (p-value 0.00). However, patients with hypercalcemia and multiple myeloma were also found to have lower odds of cord compression, although the result was not significant (OR 0.9) (P- value >0.9).

The presence of hypercalcemia in the patients was also associated with a higher cost of hospitalization compared to those who had normal calcium levels ($105035 vs $81697). It also increased the length of stay by nine days (compared to seven days for patients without hypercalcemia).

Table 2 presents a comparison of mortality and other outcomes between multiple myeloma (MM) patients with hypercalcemia and those without hypercalcemia. Figure 3 is a forest plot showing the odds ratio of outcomes in patients who had hypercalcemia in multiple myeloma.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcomes** | **With Hypercalcemia** | **Without Hypercalcemia** | **Odds ratio (OR)** | **P-value** | **Confidence Interval (95%)** |
| Mortality (%) | 6.2 | 4.8 | 1.3 | 0.00 | 1.2-1.5 |
| Length of Stay (Days) | 9 | 7 | 3.0 | 0.00 | 2.1-4.2 |
| Hyperkalemia (%) | 1.4 | 0.7 | 1.8 | 0.00 | 1.5-2.3 |
| Metabolic acidosis (%) | 17 | 12 | 1.4 | 0.00 | 1.3-1.5 |
| Acute Kidney injury (%) | 67 | 30.8 | 5.1 | 0.00 | 4.8-5.4 |
| Spinal Cord Compression (%) | 0.08 | 0.07 | 0.9 | 0.9 | 0.4-2.2 |

**Table 2 compares mortality and outcomes in MM patients with and without hypercalcemia.**

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**Figure 3 showing Odds Ratio of Adverse Events in Patients with Hypercalcemia and Multiple Myeloma**

**Discussion**:

Hypercalcemia of malignancy is an unfavorable prognostic indicator1. (ref; 1 Boa). It is narrated more frequently in multiple myeloma, and about 13-17% of newly diagnosed MM (NDMM) patients have hypercalcemia (3,4). The osteolytic bone lesions causing bone resorption with the help of nuclear factor Kappa B ligand (RANKL), interleukin six, and tumor necrosis factor are the contributors to hypercalcemia in MM (4,5). Serum calcium was part of the initial MM staging system in 1975 (6) and thought to be associated with bad outcomes; however, the international and revised international prognostic scoring systems in 2005 (7) and 2015 (8) didn't include serum calcium for staging purposes.

A study done in 2020 showed that out of 357 patients with multiple myeloma, 16.5% had hypercalcemia at the time of diagnosis (4). Our analysis showed that out of multiple myeloma patients who were admitted, 8.6% (37,765 patients) had hypercalcemia.

Elderly patients tend to have higher co-morbidities, which invariably causes poor prognosis in the MM (9). In general, the average age at MM diagnosis is 70 years. Among our cohort, the average age of MM patients was 69 years, which was similar.

In 2024, the estimated number of cases of MM among the male US population is 19,520 compared to 16,260 in females (10). Although females tend to have adverse lesions such as t(14;16) and del (17p), the Overall survival remains similar between the sexes (11). In one study, hypercalcemia is more prevalent among males than females (56.5% vs. 43.5%) (12). In another study, Li Bao et al. found that 57% (n=34) of the hypercalcemia patients were males(1). Our analysis also showed hypercalcemia is more prevalent among males ( 55%) than females (45%).

African American males are at higher risk of developing MM than Caucasian males (16.5/100,000 vs. 8.2/100,000) (13). In our analysis, the white race had a higher incidence of hypercalcemia with multiple myeloma (60%), followed by African Americans and Hispanics.

In a large MM cohort (n=196,433), 69% (n=135,678) of the patients were treated at the larger-bed hospitals (14). Similarly, 73% (n=143,885) of patients were treated at a teaching hospital (14). In our analysis, large-size hospitals, mostly tertiary care academic centers in the US, treated 54% of MM patients with hypercalcemia, likely related to a higher patient population getting treatment at these centers.

**5. Cost of hospitalization and length of stay**

Multiple myeloma (MM) tends to cause more financial burdens than other malignancies, and its costs are on the rise.(15,16)

Yang et al. compared cost analysis in double (n=1016, 66.8%) and triple class (n=505,33.2%) exposure MM patients from 2015-2019. Hospital-based ambulatory settings incurred the highest cost, $7302 (95%, $6801-$7784) per monthly patient (17). In another analysis, most of the cost is due to drugs and their infusion, $450,952 per patient.(18)

In our analysis, the presence of hypercalcemia raised the hospitalization costs to $105035, which was much higher than the patients who did not have multiple myeloma ($81697).

The length of stay was increased due to the presence of hypercalcemia. One retrospective analysis performed using NIS 2015, which included 17264 admissions of multiple myeloma, showed mean LOS was 7.22 days (SD: 7.56, Median five days) (19). Our analysis also showed without hypercalcemia, LOS was seven days. The presence of hypercalcemia, which indicated an advanced disease, increased the LOS to 9 days.

**1. Survival:**

Bao et al. (2020) showed poor survival in 357 NDMM patients who had hypercalcemia (n=60) vs. patients with average calcium level (n=297) (36.3 months vs. 56.8 months, p =0.019) and hypercalcemia remained independent poor prognostic factor with hazard ratio (HR) of 1.84, 95% CI: 1.006-3.415, p=0.048( 1). In addition, Zagouri et al. showed a worse prognosis among MM patients with hypercalcemia with a median survival of 26 months vs. 48 months, p=<0.001. After adjusting for age, ISS stage, LDH, renal function, anemia, and thrombocytopenia, hypercalcemia (Ca= >11 mg/dl) remains an adverse prognostic factor for mortality with HR of 1.32, 95% CI 1.16-1.52, p=<0.001 (20). Our analysis confirms the previous studies' results of worsening outcomes among MM patients with hypercalcemia with HR for death at 1.3, p=0.00.

**4. AKI:**

Acute kidney injury (AKI) has been known to cause poor prognosis in MM. Severe AKI is associated with a short life span of about ten months (21) (Ref 16, Haynes) Light-chain immunoglobulin is the main culprit in developing acute kidney injury in MM patients.17 (Ref; 17 Shah) Paraprotein-mediated neurotoxicity, along with prerenal azotemia, hypercalcemia, and tumor lysis, are likely reasons for AKI in MM (22). Development of AKI is associated with worse outcomes (OR 1.48, 95% CI, 1.34-1.64, p=<0.0001(14). Our analysis shows hypercalcemia causes more AKI and could potentially cause worse outcomes among MM patients with hypercalcemia.

**2. Hyperkalemia:**

As mentioned above, hypercalcemia in Multiple myeloma can affect the kidneys. Renal failure often leads to elevated potassium levels. In our analysis, we found that the patients with multiple myeloma who had hypercalcemia also had hyperkalemia (OR 1.8, p-value 0.00). This is likely due to the kidneys' impaired ability to regulate electrolyte balance, including potassium levels. We could not find other studies that reported the incidence of hyperkalemia in multiple myeloma patients.

**3. Metabolic acidosis**

In malignancies, metabolic acidosis can occur due to elevated lactic acid levels. Lactic acidosis can occur due to high tumor burden and is an indication of immediate treatment. Metabolic acidosis in multiple myeloma can be due to several factors, including renal insufficiency, lactic acidosis, and distal renal tubular acidosis (22). In our analysis, the presence of hypercalcemia in MM patients indicated advanced disease. Hence, 17% of the patients had also developed metabolic acidosis ( P-value <0.05). This result indicated that hypercalcemia in multiple myeloma indicates advanced multiple myeloma, and patients need immediate treatment to prevent worse outcomes.

**7. Spinal cord compensation**

Spinal cord compression is a medical emergency that can occur in some patients with multiple myeloma. In one study, 50.7% of the patients had multiple myeloma, and 7.8% had spinal cord compression (23). Our study found that hypercalcemia was associated with a decreased risk of spinal cord compression, although this result was not significant (p-value>0.05).

**10. Limitations of the study:**

Although our study reports significant results, there are certain limitations. This is a retrospective study, and data is obtained from records. The accuracy of the data relies on the medical records' documentation, which may vary in completeness and reliability. The findings may need to be more generalizable to other populations or settings, as the study focuses on patients admitted to hospitals in the United States during a specific period. Our study may only address some relevant factors or outcomes related to hypercalcemia in multiple myeloma.

**Conclusion**:

In conclusion, Hypercalcemia serves as an unfavorable prognostic indicator in multiple myeloma. The study helps us evaluate hypercalcemia's incidence and impacts in multiple myeloma patients. It causes increased mortality, Length of stay, and hospital charges. The study's retrospective nature and reliance on medical records pose limitations, and its findings may be somewhat generalizable. More research is required to evaluate further the effect of hypercalcemia on hospitalized patients with multiple myeloma.

**Conflict of Interest:**

The authors declare that they have no conflict of interests.

**Ethical statement**

The protocol was submitted to the Institutional Review Board (IRB), approval was waived as the database contains no patient-specific information. As it is a de-identified database, neither patients nor the public were involved in the design or planning of this project**.**

**Data Availability**

Data obtained from the Nationwide Inpatient Sample (NIS) was utilized for the research described in the article

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