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Original Article

Survival Outcomes in Malignancy-related Hypercalcemia: A Tertiary Care Single-center Experience

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Abstract

Introduction: Malignancy-related hypercalcemia is commonly observed in patients with advanced stages of cancer. It is intricately linked with an unfavorable prognosis among oncology patients. This study aimed to evaluate survival outcomes among individuals diagnosed with hypercalcemia associated with malignancy. **Materials and Methods:** This retrospective analysis of 173 cancer patients with hypercalcemia who sought treatment at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, between July 2019 and June 2020. This cohort of patients underwent a longitudinal follow-up for 2.5 years. To assess survival outcomes, the Kaplan–Meier tool was used to construct survival curves and estimate the survival probability over time. The significance of potential survival factors was evaluated using the log-rank test. **Results:** All patients exhibited elevated levels of calcium. At admission, the cohort demonstrated varying degrees of hypercalcemia severity attributable to malignancy: Mild hypercalcemia was observed in approximately 61.3% of patients, moderate hypercalcemia in 23.7%, and severe hypercalcemia in 15% of cases. Among the total sample, most patients were female (54.9%), with a median age of 54. The primary tumor site most frequently observed was in cases of breast cancer (35.3%), wherein the prevalent histological subtype was lobular/ductal invasive carcinoma (34.1%). Most of the patients (93.6%) had an Eastern Cooperative Oncology Group (ECOG) performance status (ECOG) >1. In addition, the median overall survival for patients diagnosed with hypercalcemia was 51 days. Notably, there was a significant association between survival factors, including the primary site of malignancy (P = 0.001), bone metastasis (P = 0.04), severity and symptoms of hypercalcemia (P = 0.001), altered mental state (P = 0.001),

albumin levels (P = 0.001), and ECOG (P = 0.001). **Conclusion:** Malignancy-related hypercalcemia in patients with cancer is a significant predictor of an unfavorable prognosis. The aforementioned survival factors may have the potential to influence patient survival outcomes. Further studies on larger cohorts are warranted.

Keywords: Cancer; hematological malignancies; hypercalcemia; survival outcomes

Introduction

Cancer-related hypercalcemia is a common occurrence in patients with advanced cancer, affecting approximately 20–30% of individuals.[1] This condition, known as hypercalcemia of malignancy, refers to elevated calcium levels in the bloodstream beyond the normal range.[2-4] Unfortunately, hypercalcemia of malignancy is associated with a poor prognosis in cancer patients.[1]

Among hospitalized patients, malignancy-related hypercalcemia is the most prevalent cause, affecting both those with solid tumors and hematologic malignancies.[1] Various types of cancer are commonly associated with hypercalcemia of malignancy, including breast, multiple myeloma, squamous cell carcinomas, lung, renal, and ovarian cancer, and certain lymphomas.[2]

Symptoms of hypercalcemia can range in severity from mild to potentially life-threatening.[1] These symptoms include fatigue, constipation, increased urine output (polyuria), and excessive thirst (polydipsia). Typically, mild-to-moderate hypercalcemia is observed during the early stages.[5] However, as the condition progresses, more serious complications may arise, such as cognitive dysfunction, kidney failure, and abnormal heart rhythms (arrhythmias). These severe manifestations often occur when calcium levels rise rapidly or when severe hypercalcemia is present.[5]

The pathophysiology underlying the hypercalcemic crisis involves several mechanisms.[6] First, there can be the production of parathyroid hormone (PTH)-related peptides. They bind to the same receptors as PTH, stimulate osteoclasts, and release calcium into the bloodstream. In addition, bone metastases can release factors that activate osteoclasts, leading to bone resorption and subsequent calcium release. Finally, an excessive production of calcitriol, the active form of Vitamin D, can occur, enhancing intestinal calcium absorption and further contributing to elevated calcium levels.[6]

Hypercalcemia treatment options include IV hydration, calcitonin, bisphosphonates, denosumab, gallium nitrate, prednisone, and hemodialysis.[7] IV hydration helps increase urine production and excretion of excess calcium.[8] Calcitonin inhibits bone resorption,[9-11] while bisphosphonates reduce calcium release from bones and block osteoclastic activity.[12,13] Denosumab targets osteoclast activity,[14,15] and gallium nitrate directly interferes with bone resorption.[16,17] Glucocorticoids such as prednisone inhibit calcium release and promote renal excretion.[18,19] In severe cases, hemodialysis may be used.[20,21] Treatment choice depends on factors such as severity and underlying causes.

Considering the limited number of studies examining the influence of cancer treatment on the prognosis of patients with hypercalcemia,[22-25] our objective was to assess survival outcomes in individuals with malignancy-related hypercalcemia.

Materials and Methods

The Institutional Review Board of Shaukat Khanum Memorial and Cancer Hospital and Research Centre, Pakistan, approved this retrospective study (#EX-19-05-20-04) and granted the waiver for informed consent, which follows the Declaration of Helsinki.

This retrospective analysis included patients who presented at Shaukat Khanum Memorial and Cancer Hospital and Research Centre, Lahore, between July 2019 and June 2020 with hypercalcemia. The

study focused on patients whose hypercalcemia was attributed to an underlying malignancy and identified by the hospital information system (HIS) medical record.

To be included in the analysis, patients had to meet the following criteria: Be above 18 years of age, have biopsy-proven solid or hematological malignancies, and have elevated levels of corrected calcium >10.5 mg/dL (normal range 8.5–10.5), total calcium >10.5 mg/dL (normal range 8.8–10.2), or ionized calcium is >5.5 mg/dL or 1.4 mmol/L (normal range 1.15–1.35) with low or normal levels of PTH. Patients with hypercalcemia unrelated to malignancy, such as those with primary hyperparathyroidism, sarcoidosis, or chronic kidney disease with a glomerular filtration rate <30 mL/min/1.73 m² before the onset of hypercalcemia, were excluded from the study. The final data analysis was conducted on 173 patients [Table 1]. This cohort of patients was subjected to a longitudinal follow-up for 2.5 years, culminating on December 15, 2022. Data regarding patients' clinicopathological and radiological parameters were retrieved from the HIS medical records. The acquisition of patient data adhered to applicable data protection and privacy regulations.

Table 1: Flowchart of malignancy-related hypercalcemia patients admissions at SKMCH&RC (July 2019 to June 2020)

Category	Count
Total patients presented with hypercalcemia from July 2019 to June 2020	298
Excluded patients (other causes)	81
- Primary hyperparathyroidism	
- Multiple endocrine neoplasia syndrome	
- Chronic kidney disease with GFR < 30 ml/min/1.73 m²	
Admitted with symptomatic malignancy-related hypercalcemia	217
Lost to follow up among malignancy-related hypercalcemia	44
Followed till 15th Dec 2022	173
- Died	150
- Alive till last follow up	23

We categorized the severity of hypercalcemia into three categories. Mild hypercalcemia was identified when total calcium ranged from 10.5 to 11.9 mg/dL or corrected calcium ranged from 10.5 to 11.9 mg/dL or ionized calcium ranged from 5.6 to 8 mg/dL or 1.4 to 2 mmol/L. Similarly, moderate hypercalcemia had target ranges of total calcium 12–13.9 mg/dL or corrected calcium 12–13.9 mg/dL or ionized calcium 8–10 mg/dL or 2–2.5 mmol/L. Severe hypercalcemia occurs when total calcium is more than 14 mg/dL or corrected calcium is 14 mg/dL or ionized calcium is more than 10 mg/dL or 2.5 mmol/L. The laboratory variables for the patients were determined using identical kits, as illustrated in Table 2.

In this study, the overall survival (OS) was defined as the time interval from the first episode of hypercalcemia until death. Individuals who were still alive were followed until December 15, 2022. Survival factor refers to any variable or characteristic that has a significant impact on the survival outcomes of cancer patients with hypercalcemia.

Statistical analysis

Statistical analysis was done using the Statistical Package for the Social Sciences software version 26.0 (IBM Corp., Armonk, NY, USA). Mean and standard deviation or median and range were presented for quantitative/continuous variables. Frequency and percentages were reported for qualitative/categorical variables. Survival curves were generated using the Kaplan–Meier tool to estimate the probability of survival over time. The survival difference between different factors was assessed using the log-rank test. Variables that yielded a $P < 0.05$ were considered statistically significant and were associated with worse outcomes.

Results

Patient characteristics

Table 2 presents the characteristics of the patients included in the study. The majority of the patients were female, accounting for 54.9% of the total

Table 2: Demographics and clinicopathological characteristics of the patients included in the study

Demographics	Number (%)
Gender	
Male	78 (45.1)
Female	95 (54.9)
Median Age, years (Range)	54 (22–95)
Histology	
Squamous cell carcinoma	49 (28.3)
Adenocarcinoma	13 (7.5)
Lobular/ductal invasive	59 (34.1)
Lymphoma	16 (9.2)
Multiple myeloma	8 (4.6)
Others	28 (16.2)
Primary site of malignancy	
Head and neck	21 (12.1)
Lung	14 (8.1)
Breast	61 (35.3)
Gastrointestinal	18 (10.4)
Hematology	23 (13.3)
Others	36 (20.8)
ECOG PS	
1	11 (6.4)
2	50 (28.9)
3	63 (36.4)
4	49 (28.3)
Bone metastasis	
Yes	122 (70.5)
No	51 (29.5)
Type of bone metastasis	
Vertebral and non-vertebral metastasis	77 (44.5)
Vertebral	25 (14.5)
Non-vertebral	20 (11.6)
None	51 (29.5)
Symptoms	
Altered mental State	67 (38.7)
Bony aches	77 (44.5)
Constipation	5 (2.9)
Fatigue	24 (13.9)
Liver metastasis	
Yes	66 (38.2)
No	107 (61.8)
Severity of hypercalcemia	
Mild	106 (61.3)
Moderate	41 (23.7)
Severe	28 (15.0)
Type of malignancy	
Solid	148 (85.5)
Hematological	23 (13.3)
Laboratory variables	**Median (Range)**
Hemoglobin, (12–15 g/dL)	10.5 (0–16)
C-reactive protein, (<5 mg/L)	9 (0–481)
Albumin, (3.5–5.2 g/dL)	3.11 (0–5.06)
BMI, kg/m^2	24.22 (0–44.9)
GFR, (>60 mL/min/73 m^2)	70.2 (0.46–984)
TLC, (4–10×10^3/uL)	10.88 (0.73–99)
Platelet, (150–450×10^3/uL)	274 (0–681)
Creatinine, (0.50–0.90 mg/dL)	0.88 (0–211)
Alkaline phosphatase, (35–104 u/L)	139.77 (36.29–2953)
Magnesium, (1.6–2.4 mg/dL)	1.78 (0–296)
Sodium, (136–145 mmol/L)	136 (0–174)
Potassium, (3.5–5.5 mmol/L)	4.38 (2.57–145)
Parathyroid hormone, (18.5–88 pg/mL)	8.1 (4.6–86)
Vitamin D, (40–100 ng/mL)	19.1 (8.7–73.5)
Phosphate levels, (2.5–4.5 mg/dL)	3.4 (1.6–8.4)
Hypercalcemia	**Number (%)**
MILD: (total calcium 10.5–11.9 mg/dL or Corrected calcium 10.5–11.9 mg/dL or ionized Calcium 5.6–8 mg/dL or 1.4–2 mmol/L)	106 (61.3)
MODERATE: (total calcium 12–13.9 mg/dL or Corrected calcium 12–13.9 mg/dL or ionized Calcium 8–10 mg/dL or 2–2.5 mmol/L)	41 (23.7)
SEVERE: (total calcium >14 mg/dL or Corrected calcium >14 mg/dL or ionized Calcium >10 mg/dL or >2.5 mmol/L)	26 (15)

ECOG PS: Eastern Cooperative Oncology Group performance status, BMI: Body mass index, GFR: Glomerular filtration rate, TLC: Total leukocyte count

sample, with a median age of 54 years. The most common histological subtype observed was lobular/ductal invasive carcinoma, representing 34.1% of the cases, followed by squamous cell carcinoma, which was found in 28.3% of the patients.

In terms of the primary tumor sites, breast cancer was the most frequently observed, accounting for 35.3% of the cases. Hematological malignancies accounted for 13.3% of the cases, and head and neck cancers were identified in 12.1% of the patients. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was evaluated to assess the patient's overall health and functional status at admission with hypercalcemia. A vast majority of the patients, 93.6%, had an ECOG PS score > 1, indicating a significant impact of the disease on their daily activities. Patients presenting with ECOG PS 1 accounted for 6.4%, those with ECOG PS 2 constituted 28.9%, while individuals with ECOG PS 3 and 4 comprised 36.4% and 28.3%, respectively, at the time of admission.

Bone metastasis was prevalent in the study cohort [Figure 1], observed in 122 (70.5%) patients. Among these patients, 77 (44.5%) had both vertebral and non-vertebral metastasis, whereas 25 (14.5 %) had only vertebral metastasis and 20 (11.6%) had non-vertebral metastasis.

The most common presenting symptom of malignancy-related hypercalcemia was bony aches, reported by 77 patients (44.5%). The altered mental state was also a significant presenting symptom observed in 66 patients (38.7%). Furthermore, the prevalence of hypercalcemia was found to be higher in patients with solid malignancies, with 85.5% of these patients experiencing elevated levels of calcium in their blood. This finding suggests a higher propensity for hypercalcemia in patients with solid tumors than other malignancies. Almost 61.3% of patients were admitted with mild hypercalcemia, whereas 23.7% had moderate and 15% had severe hypercalcemia of malignancy at the time of admission. In addition, Table 2 provides the reference ranges for the remaining laboratory variables.

Survival outcomes

We conducted a follow-up of the patients until December 15, 2022. Among the initial 173 patients included in the study, a significant majority of 150 patients (86.7%) died. In comparison, only 23 patients (13.3%) remained alive until the last follow-up, as depicted in Table 3. The data revealed that a substantial proportion of patients, 39.9%, passed away within the first 30 days of presentation, followed by 12.7% in the 2nd month and 8.7% in the 3rd month. In addition, 25.4% of patients experienced mortality beyond 3 months from their initial presentation. The median OS for the patients was found to be 51 days, indicating that approximately half of the total patients passed away within 51 days of hypercalcemia presentation, with a range of 31–70 days, as shown in Figure 2. These findings highlight that hypercalcemia in cancer patients is associated with survival outcomes.

We investigated several factors such as histopathology, the presence of bone metastasis, the severity of hypercalcemia, symptoms of hypercalcemia, altered mental state, ECOG performance status, albumin levels, the primary site of malignancy, presence of hepatic metastasis, type of malignancy (solid or hematological), and site of bony metastasis, as presented in Table 4. The *P*-values for the examined variables, such as ECOG, altered mental state, albumin, primary site, severity, histopathology, bone metastasis, and symptoms, all were below the 0.05 threshold. This indicates a statistically significant survival difference associated with these factors. In addition, variables featuring more than two categories possess clinical significance. However, it is essential to note that the statistical significance applies to the variables and not necessarily among their individual categories.

To evaluate the impact of specific factors on patient survival, cutoff values were established for certain variables, such as ECOG > 2, C-reactive protein (CRP) > 30 mg/dL, albumin < 2.5 g/dL, and body mass index (BMI) < 18 kg/m^2. Analysis revealed that patients with squamous cell carcinoma had a median OS of 30 days. In contrast, lymphoma exhibited the highest median OS of 334 days, as depicted in Figure 3a. A notable disparity was observed among patients with bony metastasis, with a better median OS [Figure 3b]. Among

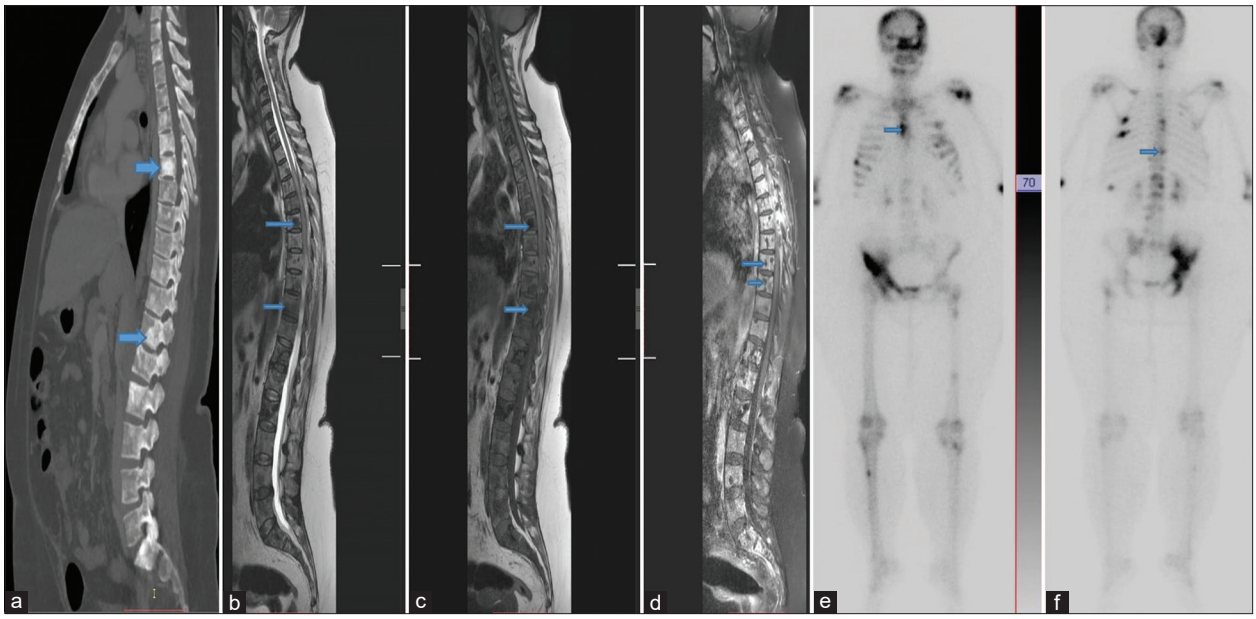

Figure 1: Radiological representative images of bone metastasis: Images of a 50-year-old female patient of breast cancer with extensive axial skeleton osseous metastasis. Magnetic resonance imaging whole spine (a) T2 weighted, (b) T1 weighted, (c) contrast-enhanced mid-sagittal slices, (d) computed tomography scan mid-sagittal slice, bone window settings, and (e and f) Bone scan, anterior and posterior planer images. Blue arrows are sites of axial skeleton osseous metastasis.

Table 3: Survival outcome of the patients included in this study

Status	Number (Percentage)
Dead	150 (86.7)
Alive	23 (13.3)
Death within days	**Number (Percentage)**
Within 30 days	69 (39.9)
30–60 days	22 (12.7)
60–90 days	15 (8.7)
>90 days	44 (25.4)

Only 23 (13.3%) remained alive till the last follow-up

patients admitted with severe hypercalcemia, the median OS was only 13 days, which increased to 61 days for moderate hypercalcemia cases and 73 days for mild hypercalcemia cases [Figure 3c]. In addition, patients exhibiting an altered mental state demonstrated a significantly reduced median OS of 13 days. Furthermore, it was identified as an independent and unfavorable factor, irrespective of the severity of hypercalcemia. In contrast, patients presenting with constipation (62 days), fatigue (91 days), or bony aches (117 days) demonstrated relatively better median OS [Figure 3d and e]. Notably, cardiac complications were not observed in this cohort. Patients with an ECOG performance status >2 at admission had an overall median survival of only 25 days (range: 8.5–41.4 days), while those with an ECOG performance status <2 exhibited a median OS of 140 days [Figure 3f]. Furthermore, malnourished patients with albumin levels below 2.5 g/dL had a median OS of 23 days, which improved to 64 days for patients with albumin levels above 2.5 g/dL at admission [Figure 3g]. Among the different malignancies examined, there were notable variations in median OS. Head and neck malignancies had the lowest median OS, with only 13 days, while gastrointestinal malignancies demonstrated a slightly longer median OS of 23 days. Conversely, hematological malignancies exhibited a significantly better survival, with a more favorable median OS of 405 days, as illustrated in Figure 3h.

In contrast to these factors, no significant differences were observed in variables such as CRP levels, BMI,

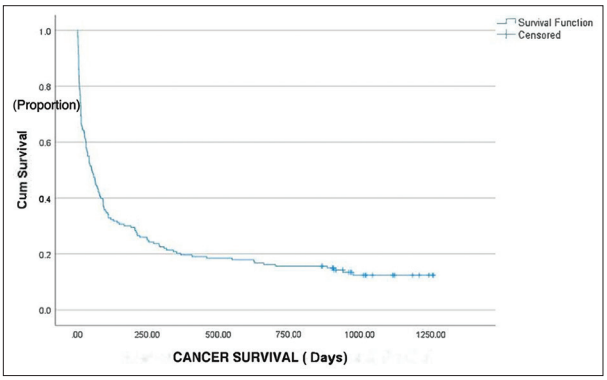

Figure 2: The median overall survival (OS) for the patients was found to be 51 days. X-axis: Cancer survival days. Y-axis: Cumulative survival proportion. The median OS curve represents the relationship between the onset of hypercalcemia and the proportion of patients who survive beyond that time. X-axis represents the time (number of days) from the onset of hypercalcemia till death. Y-axis represents the cumulative proportion of patients who survive beyond a certain time point. Curve starts at 1 (100 %) on Y-axis indicating that all patients are alive at the beginning of the study. As time progresses, the curve descends gradually, reflecting the decrease in the proportion of patients surviving as time goes on. Median OS represents the time at which 50 % of patients have survived beyond. Median OS was 51 days (95% confidence interval 31–70 days)

presence of liver metastasis, and type of bone metastasis. These factors did not show substantial associations with variations in median OS.

Discussion

In this single-center retrospective study, the median OS for the patients was found to be 51 days, indicating that approximately half of the total patients passed away within 51 days of hypercalcemia presentation, with a range of 31–70 days. Among the initial 173 patients included in the study, a significant majority of 150 patients (86.7%) died. In comparison, only 23 patients (13.3%) remained alive until the last follow-up. Our data revealed that a substantial proportion of patients, 39.9%, passed away within the first 30 days of presentation. These findings highlight the significant impact and limited survival rates associated with hypercalcemia, as reported by previous studies.[25-27]

Malignancy-related hypercalcemia is a significant concern due to its prominent role as the leading cause of hypercalcemia and its substantial impact on the prognosis of individuals with cancer.[28] The prognosis of malignancy-related hypercalcemia is influenced by several factors, including the underlying cause and the specific type of cancer.[29] Early-stage diseases generally tend to have a more favorable prognosis. In contrast, advanced stages or delayed diagnosis of hypercalcemia may lead to a poorer prognosis.[29] This condition is observed in approximately 20% of cancer patients as their disease progresses.[30] It can manifest with varying degrees of severity, ranging from mild symptoms to potentially life-threatening manifestations.[28] In this study, we aimed to assess survival outcomes in individuals with malignancy-related hypercalcemia.

Solid tumors were more frequently treated at our hospital than hematological malignancies. Within our dataset, patients with hematological malignancies constituted 13.3%, while those with non-hematological malignancies comprised 85.5%. Interestingly, we noted no significant difference in OS between these two categories.

Our study identified several factors associated with survival outcomes in patients with malignancy-related hypercalcemia. Among our dataset, breast cancer was the most prevalent primary tumor site, accounting for 35.3% of cases, with lobular/ductal invasive carcinoma being the predominant histological subtype at 34.1%. These findings were consistent with a study conducted by Soyfoo *et al*., where breast cancer was also reported as the most frequent site (29%).[31] However, contrasting results were reported in the European series by Penel *et al*., which found the head and neck region to be the most frequent primary site.[26,27] The onset of hypercalcemia in cancer patients with well-differentiated neuroendocrine neoplasms poses a significant clinical challenge with a notable tendency for it to go undiagnosed.[32,33] Among its causes, systemic secretion of PTH-related protein and ectopic production of 1,25-dihydroxyvitamin D

Table 4: Relationship between various factors and survival outcomes was investigated

Factor	Median OS, days (range)	*P*-value
ECOG		**<0.001**
>2	25 (8.5–41.4)	
≤2	140 (2.2–277.7)	
Altered mental state		**<0.001**
Yes	13 (10.3–15.6)	
No	108 (24.7–191.24)	
C-reactive protein		0.06
>30	30 (0.00–67.9)	
<30	245 (193.8–296.1)	
Albumin		**<0.001**
<2.5	23 (0.0–50.1)	
>2.5	64 (37.0–90.9)	
BMI		0.75
<18	36 (33.0–38.9)	
>18	52 (30.6–73.3)	
Primary site of malignancy		**<0.001**
Head and neck	13 (4.0–21.9)	
Lung	82 (48.9–115.0)	
Breast	89 (63.8–114.1)	
Gastrointestinal	23 (0.1–45.8)	
Hematological	405 (0–1151.5)	
Others	30 (0–63.8)	
Severity of hypercalcemia		**<0.001**
Mild	73 (38.3–107.6)	
Moderate	61 (32.1–89.8)	
Severe	13 (6.7–19.2)	
Type of malignancy		0.31
Solid	43 (19.1–66.8)	
Hematological	405 (0–1151.5)	
Histopathology		**<0.001**
Squamous cell carcinoma	30 (5.3–54.6)	
Adenocarcinoma	52 (0–116.5)	
Ductal/lobular invasive	89 (64.2–113.7)	
Lymphoma	334 (0–1013.2)	
Multiple myeloma	69 (0–0)	
Others	18 (0–47.8)	
Bone metastasis		**0.045**
Yes	63 (33.6–92.3)	
No	36 (23.7–48.2)	
Types of bone metastasis		0.21
Both	76 (48.9–103)	
Vertebral	26 (5.6–46.3)	

(Contd...)

Table 4: ***(Continued)***

Factor	Median OS, days (range)	*P*-value
Non-vertebral	51 (0–108.9)	
None	36 (24.3–47.6)	
Symptoms		**<0.001**
Altered mental state	13 (9.0–16.9)	
Bony aches	117 (23.3–210.6)	
Constipation	62 (16.9–107)	
Fatigue	91 (15.9–166)	
Liver metastasis		0.102
Yes	41 (13.1–68.8)	
No	61 (28.7–93.2)	

ECOG PS: Eastern Cooperative Oncology Group performance status, Median OS: Median overall survival, BMI: Body mass index. A *P*-value below 0.05 was considered statistically significant, Bold values represent statistically significant results.

and PTH may be considered paraneoplastic causes of hypercalcemia.[33]

Patients with gastroenteropancreatic-neuroendocrine tumors face an elevated risk of osteopenia and osteoporosis due to various factors affecting bone metabolism.[34] In our dataset, we identified only two patients with neuroendocrine tumors. A study conducted by Degardin *et al*. revealed that performance status significantly impacts patients' survival.[35] We also identified that patients with an ECOG performance status >2 at admission had an overall median survival of only 25 days. Our results are in compliance with the previously published data by Ramos *et al*.[25] In addition, hypoalbuminemia was identified as a predictor of poor survival by Penel *et al*.[26] We also observed that malnourished patients with albumin levels below 2.5 g/dL had a median OS of only 23 days which was less than the median OS identified by Ramos *et al*.[25]

Patients with an altered mental state, symptoms, and severity experienced shorter median OS in our findings indicating the poor survival outcomes which are in accordance with the previous studies.[25,26] While Penel *et al*. identified bone metastasis as a factor associated with poor survival,[26] we found that bone metastasis was not linked to worse outcomes. Our findings highlight the importance of considering these factors when assessing survival outcomes in patients with malignancy-related hypercalcemia.

The present study is constrained by certain limitations stemming from its retrospective design. A noteworthy constraint involves the relatively modest sample size employed in this investigation. It is essential to highlight that a majority of the participants in this study exhibited solid malignancies, as opposed to hematological malignancies. We followed the international guidelines for managing malignancy-related hypercalcemia, and the administration of treatments such as zoledronate and pamidronate was carried out based on the discretion of the treating physicians. Unfortunately, specific details regarding the treatment process were not systematically documented, rendering us unable to discern the impact of these medications on the current survival outcomes. Moreover, it is pertinent to emphasize that, to the best of our knowledge; this study stands as a pioneering endeavor in Pakistan. It represents the first comprehensive investigation encompassing both solid tumors and hematologic malignancies in Pakistan.

Malignancy-related hypercalcemia in cancer patients predicts unfavorable survival outcomes. The factors associated with malignancy-related hypercalcemia hold promise for potentially influencing patient survival outcomes. However,

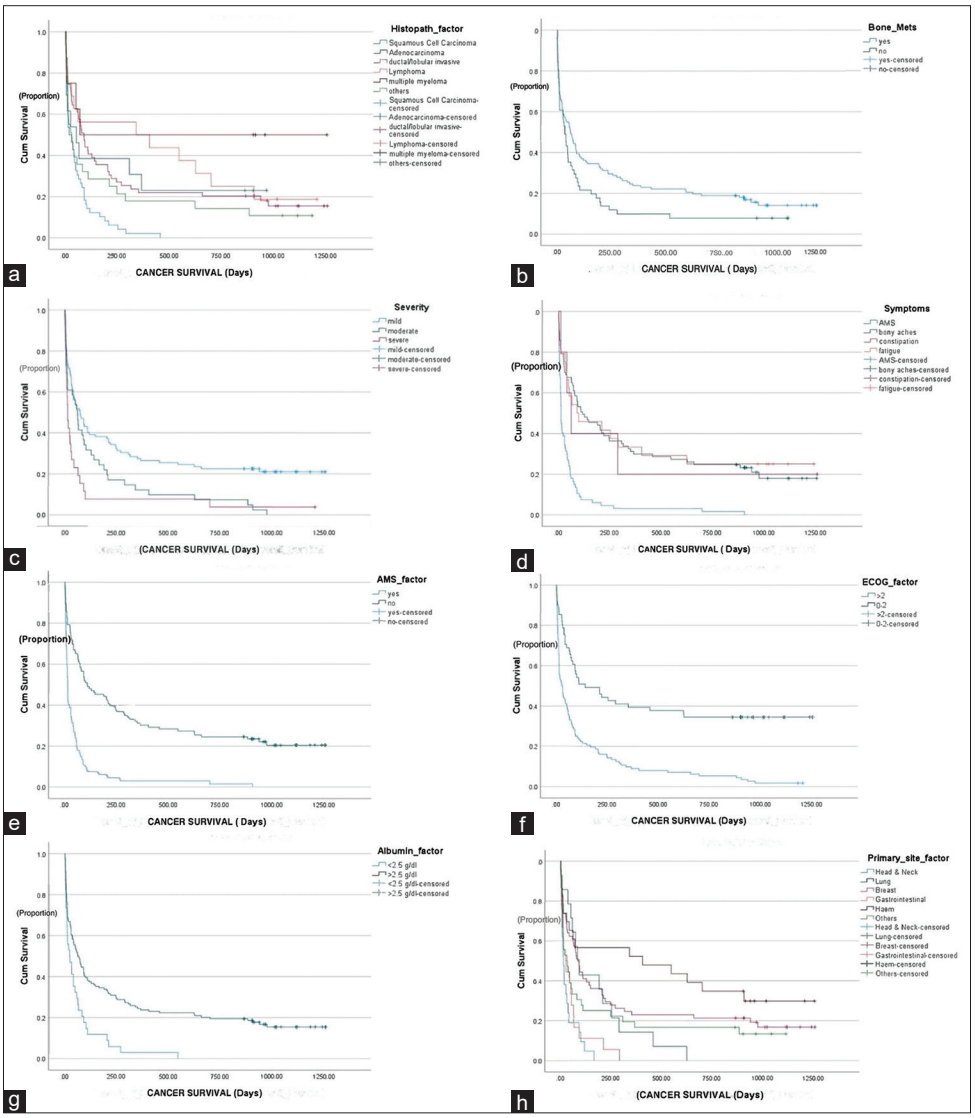

Figure 3: Impact of various factors on overall survival (OS) was determined: (a) Delineated significant variance in OS across distinct histopathologies ($P < 0.001$). Squamous cell carcinoma exhibited better long-term survival compared to adenocarcinoma, ductal/lobular invasive, lymphoma, multiple myeloma, and others. In (b), the illustration depicted a notable survival discrepancy between groups based on the presence or absence of bone metastasis ($P < 0.04$). (c) Elucidated the gradation of hypercalcemia severity (mild, moderate, and severe) with superior OS observed in patients with mild hypercalcemia ($P < 0.001$). (d) Clarified OS differences among various reported symptoms ($P < 0.001$). (e) Illustrates the contrast in OS based on the presence or absence of altered mental state (AMS) ($P < 0.001$). In addition, (f) depicted a significant survival discrepancy across different Eastern Cooperative Oncology Group (ECOG) statuses ($P < 0.001$), with better survival rates observed in patients with ECOG statuses of 0–2 compared to those with statuses below 2. (g and h) demonstrated OS variation between albumin categories (<2.5 vs. >2.5) ($P < 0.001$) and primary cancer sites ($P < 0.001$), with marginal survival differences between albumin categories and no disparity observed among primary cancer sites

further studies involving larger cohorts are imperative to enhance our understanding and confirm these findings due to the need for more comprehensive data and a broader sample size.

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References

1. Almuradova E, Cicin I. Cancer-related hypercalcemia and potential treatments. Front Endocrinol 2023;14:1039490.
2. Jick S, Li L, Gastanaga VM, Liede A. Prevalence of hypercalcemia of malignancy among cancer patients in the UK: Analysis of the Clinical Practice Research Data link database. Cancer Epidemiol 2015;39:901-7.
3. Burt ME, Brennan MF. Incidence of hypercalcemia and malignant neoplasm. Arch Surg 1980;115:704-7.
4. Goldner W. Cancer-related hypercalcemia. J Oncol Pract 2016;12:426-32.
5. Walker MD, Shane E. Hypercalcemia: A review. JAMA 2022;328:1624-36.
6. Guise TA, Wysolmerski JJ. Cancer-associated hypercalcemia. N Engl J Med 2022;386:1443-51.
7. Mirrakhimov AE. Hypercalcemia of malignancy: An update on pathogenesis and management. N Am J Med Sci 2015;7:483.
8. Hosking DJ, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. QJM 1981;50:473-81.
9. Vaughn CB, Vaitkevicius VK. The effects of calcitonin in hypercalcemia in patients with malignancy. Cancer 1974;34:1268-71.
10. Wisneski LA. Salmon calcitonin in the acute management of hypercalcemia. Calcif Tissue Int 1990;46:S26-30.
11. Austin LA, Heath 3rd H. Calcitonin: Physiology and pathophysiology. N Engl J Med 1981;304:269-78.
12. Xu XL, Gou WL, Wang AY, Wang Y, Guo QY, Lu Q, *et al*. Basic research and clinical applications of bisphosphonates in bone disease: What have we learned over the last 40 years? J Transl Med 2013;11:1-8.
13. Russell RG, Xia Z, Dunford JE, Oppermann UD, Kwaasi A, Hulley PA, *et al*. Bisphosphonates: An update on mechanisms of action and how these relate to clinical efficacy. Ann N Y Acad Sci 2007;1117:209-57.
14. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: Mechanism of action and clinical outcomes. Int J Clin Pract 2012;66:1139-46.
15. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, *et al*. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29:1125-32.
16. Warrell RP, Bockman RS, Coonley CJ, Isaacs M, Staszewski H. Gallium nitrate inhibits calcium resorption from bone and is effective treatment for cancer-related hypercalcemia. J Clin Invest 1984;73:1487-90.
17. Cvitkovic F, Armand JP, Tubiana-Hulin M, Rossi JF, Warrell RP Jr. Randomized, double-blind, phase II trial of gallium nitrate compared with pamidronate for acute control of cancer-related hypercalcemia. Cancer J 2006;12:47-53.
18. Adams JS. Vitamin D metabolite-mediated hypercalcemia. Endocrinol Metab Clin N Am 1989;18:765-78.
19. Fardet L, Flahault A, Kettaneh A, Tiev KP, Généreau T, Tolédano C, *et al*. Corticosteroid-induced clinical adverse events: Frequency, risk factors and patient's opinion. Br J Dermatol 2007;157:142-8.
20. Koo WS, Jeon DS, Ahn SJ, Kim YS, Yoon YS, Bang BK. Calcium-free hemodialysis for the management of hypercalcemia. Nephron 1996;72:424-8.
21. Leehey DJ, Ing TS. Correction of hypercalcemia and hypophosphatemia by hemodialysis using a conventional, calcium-containing dialysis solution enriched with phosphorus. Am J Kidney Dis 1997;29:288-90.
22. Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer-associated hypercalcemia: Morbidity and mortality: Clinical experience in 126 treated patients. Ann Intern Med 1990;112:499-504.
23. Ling PJ, A'Hern RP, Hardy JR. Analysis of survival following treatment of tumour-induced hypercalcaemia with intravenous pamidronate (APD). Br J Cancer 1995;72:206-9.
24. Gupta S, Rastogi A, Singh P, Chophy A, Roushan R, Krishnan AS, *et al*. Treatment outcomes and survival in hypercalcemia of malignancy: A grave metabolic emergency. Cureus 2023;15:e35783.
25. Ramos RE, Perez Mak M, Alves MF, Piotto GH, Takahashi TK, Gomes da Fonseca L, *et al*. Malignancy-related hypercalcemia in advanced solid tumors: Survival outcomes. J Glob Oncol 2017;3:728-33.
26. Penel N, Dewas S, Doutrelant P, Clisant S, Yazdanpanah Y, Adenis A. Cancer-associated hypercalcemia treated with intravenous diphosphonates: A survival and prognostic factor analysis. Support Care Cancer 2008;16:387-92.
27. Penel N, Dewas S, Hoffman A, Adenis A. Cancer-associated hypercalcemia: Validation of a bedside prognostic score. Support Care Cancer 2009;17:1133-5.
28. Feldenzer KL, Sarno J. Hypercalcemia of malignancy. J Adv Pract Oncol 2018;9:496.
29. Vakiti A, Anastasopoulou C, Mewawalla P. Malignancy-related hypercalcemia. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2018.

30. Flombaum CD. Metabolic emergencies in the cancer patient. Semin Oncol 2000;27:322-34.
31. Soyfoo MS, Brenner K, Paesmans M, Body JJ. Non-malignant causes of hypercalcemia in cancer patients: A frequent and neglected occurrence. Support Care Cancer 2013;21:1415-9.
32. Giannetta E, Sesti F, Modica R, Grossrubatscher EM, Ragni A, Zanata I, *et al*. What lies behind paraneoplastic hypercalcemia secondary to well-differentiated neuroendocrine neoplasms? A systematic review of the literature. J Pers Med 2022;12:1553.
33. Giannetta E, Sesti F, Modica R, Grossrubatscher EM, Guarnotta V, Ragni A, *et al*. Case report: Unmasking hypercalcemia in patients with neuroendocrine neoplasms. Experience from six Italian referral centers. Front Endocrinol 2021;12:665698.
34. Altieri B, Di Dato C, Modica R, Bottiglieri F, Di Sarno A, Pittaway JF, *et al*. Bone metabolism and vitamin D implication in gastroenteropancreatic neuroendocrine tumors. Nutrients 2020;12:1021.
35. Degardin M, Nguyen M, Beaurin D, Lesoin A, Fournier C, Lefebvre JL, *et al*. Hypercalcemia and squamous cell carcinoma of the upper respiratory-digestive tracts. Incidence and prognosis. Bull Cancer 1995;82:975-80.

Authorship Contributions

Conceived and designed the analysis: SA, WS, AIS, UA, AF, KS, KA; Collected the data: SA, HI; Contributed data or analysis tools: WS, AIS, UA, HI, MAB, MH, AZS, KS, KA; Performed the analysis: SA, WS, AIS, UA, SAK, MAB, MH, AF, AZS, KS; Wrote the paper: SA, WS, AIS, UA, HI, SAK, AMA, MAB, MH, AF, AZS, KA.