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Treatment Outcomes of Hypercalcemia of Malignancy Among Advanced Cancer Patients Attending Palliative Care Unit of a Tertiary Care Hospital in Bangladesh: An Observational Study

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ABSTRACT

Background and Aim: Hypercalcemia is one of the most common complications of advanced malignancy. Treatment of hypercalcemia among advanced cancer patients often gives rise to complex ethical issues. This study aims to explore treatment outcomes of hypercalcemia among advanced cancer patients so that palliative care physicians can design cost-effective and efficient approaches to diagnosis and treatment for these patients.

Methods: This observational study was conducted among 31 advanced (stages III and IV) cancer patients diagnosed with hypercalcemia of malignancy admitted to the Department of Palliative Medicine, Bangabandhu Sheikh Mujib Medical University, Bangladesh, from June to December 2023. The patients were observed on the day of admission and followed up on 3rd and 7th day for assessment of their response to the received treatment. Chi-square test, Fisher's exact test, paired and unpaired *t*-tests were done to assess the treatment response and changes in the clinical characteristics of the patients.

Result: After 3 days of rehydration therapy, the mean serum calcium level decreased significantly from 12.43 ± 1.96 to 10.82 ± 2.07 after treatment, with a significant *p*-value of < 0.001. For the management of remaining hypercalcemic patients, intravenous bisphosphonates are used in conjunction with normal saline. There was a substantial decrease in the mean value of serum calcium level from 12.66 ± 1.91 to 10.27 ± 0.75 after treatment with normal saline and bisphosphonate on the 7th day. The majority of patients (64.5%) showed improvement following treatment. A smaller percentage (16.1%) remained hypercalcemic even after getting all treatments. Unfortunately, 19.4% died, possibly due to the progressive nature of the disease along with hypercalcemia.

Conclusion: Malignant hypercalcemia is a potentially fatal, undiagnosed, and undertreated complication of advanced malignancy. It is essential for palliative care physicians to identify hypercalcemia and develop comprehensive care plan to optimize the treatment outcomes.

1 | Background

Hypercalcemia of malignancy (HCM) is a common complication of advanced cancer. It is characterized by an elevated serum calcium level greater than 2.6 mmol/L or 10.5 mg/dL [1]. Nearly 41.3% of individuals with advanced cancer are hypercalcemic [2].

Symptoms of HCM vary depending on the level of serum calcium. Patients often exhibit gastrointestinal symptoms such as anorexia, nausea, vomiting, constipation, abdominal pain, and occasionally peptic ulcer disease [3]. Additionally, HCM can cause neurologic symptoms ranging from fatigue to coma, psychiatric symptoms including anxiety, memory loss, and depression, as well as cardiovascular symptoms such as arrhythmias and a shortened QT interval [4, 5]. The management of HCM depends on the severity of the calcium increase and the specific symptoms present. Patients suffering from HCM usually need prompt management because if left untreated, the prognosis could be fatal [6].

Treatment for HCM should be targeted precisely against the mediating pathways. Treatments include intravenous saline for hydration, bisphosphonates, calcitonin, denosumab, prednisolone, furosemide, and hemodialysis [6]. Although treatment of severe HCM in its early stages can improve symptoms, it has a limited impact on life expectancy. There are controversies regarding the appropriateness of treatment at advanced stages [7].

Treating HCM in advanced cancer patients often raises complex ethical issues. It has been suggested that aggressively treating HCM at the terminal stage may lead to futile treatment and increased patient discomfort. Most doctors (80%) from the surgical and oncological faculties believe that treating HCM alleviates distressing symptoms and improves patients' overall quality of life. However, physicians from internal medicine and palliative care are less likely to support treating HCM in the terminal phase. They argue that the treatment itself causes more suffering than the hypercalcemia and that its efficacy diminishes over time. Therefore, palliative care physicians must carefully weigh the pros and cons of treating HCM in dying patients [8].

Currently, there is a scarcity of studies regarding treatment outcomes of HCM among advanced cancer patients in palliative care settings in Bangladesh. Understanding the clinical characteristics and treatment outcomes of HCM can assist palliative care physicians in identifying cost-effective and efficient approaches to diagnosis and treatment, thereby ensuring judicious utilization of palliative care resources.

2 | Methods

2.1 | Study Design and Setting

This observational study was conducted among adult advanced cancer (stages III and IV) patients admitted to the Department of Palliative Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU) in Shahbag, Dhaka. Data collection took place from June to December 2023.

2.2 | Sample Criteria

Patients aged ≥ 18 years, diagnosed with any type of solid tumor (carcinomas or sarcomas) or hematologic malignancies (leukemia, lymphoma, and multiple myeloma) in stages III and IV, with a serum calcium level ≥ 10.5 mg/dL at admission, were included in the study. Non-cancer patients or those with HCM likely caused by conditions other than malignancy (e.g., primary hyperparathyroidism, hypervitaminosis D, or drug-induced hypercalcemia) were excluded.

2.3 | Sample Size

We determined the sample size of the study using a census method. From June to December, a total of 330 adult advanced cancer patients were admitted to our department. Among them, 31 patients had a serum calcium level ≥ 10.5 mg/dL, indicating HCM. Therefore, our final sample size for the study was 31 (Figure 1).

2.4 | Data Collection Procedure

Data were collected by the principal investigator using a well-structured questionnaire. The purpose of the study was explained to the patient and the caregivers and/or relatives and written informed consent was taken before the interview.

Within 24 h of admission, symptoms were assessed from presenting complaints, and signs were elicited by performing physical examinations. Also 5 mL of venous blood sample was collected aseptically in a vacutainer tube by the trained nurses at the department of palliative medicine. The labeled samples were then sent to the Department of Biochemistry for required tests to be done. Blood sample for biochemical analysis was analyzed by Automated Analyzer: Atellica, Simens's Germany at the biochemistry department. After that, reports were collected and noted down in the data collection form. Then corrected calcium levels of the patients were calculated using the following formula: Corrected Calcium = (0.8 × (Normal Albumin − Pt's Albumin)) + Serum Ca [9].

The corrected serum calcium level is categorized as follows: serum calcium level between 10.5 and 11.9 mg/dL is considered mild HCM, between 12 and 13.9 mg/dL is moderate HCM, and a serum calcium level ≥ 14 mg/dL is classified as severe HCM [10]. These patients were observed for the given treatment (e.g., normal saline, bisphosphonate, diuretics) directed by the palliative care team. No alteration were made to the treatment protocol by the investigators. The change in their clinical presentations was also observed for the next 3 days. On the 3rd day, hypercalcemic patients were followed up for the existing sign-symptoms of HCM, and another blood sample was sent for reanalysis for serum calcium and albumin on the same day.

For patients who became normocalcemic, treatment for HCM was stopped, but other treatments were continued. Patients who remained hypercalcemic even after getting treatment for 3 days got further management of HCM (e.g., Normal saline, steroid,

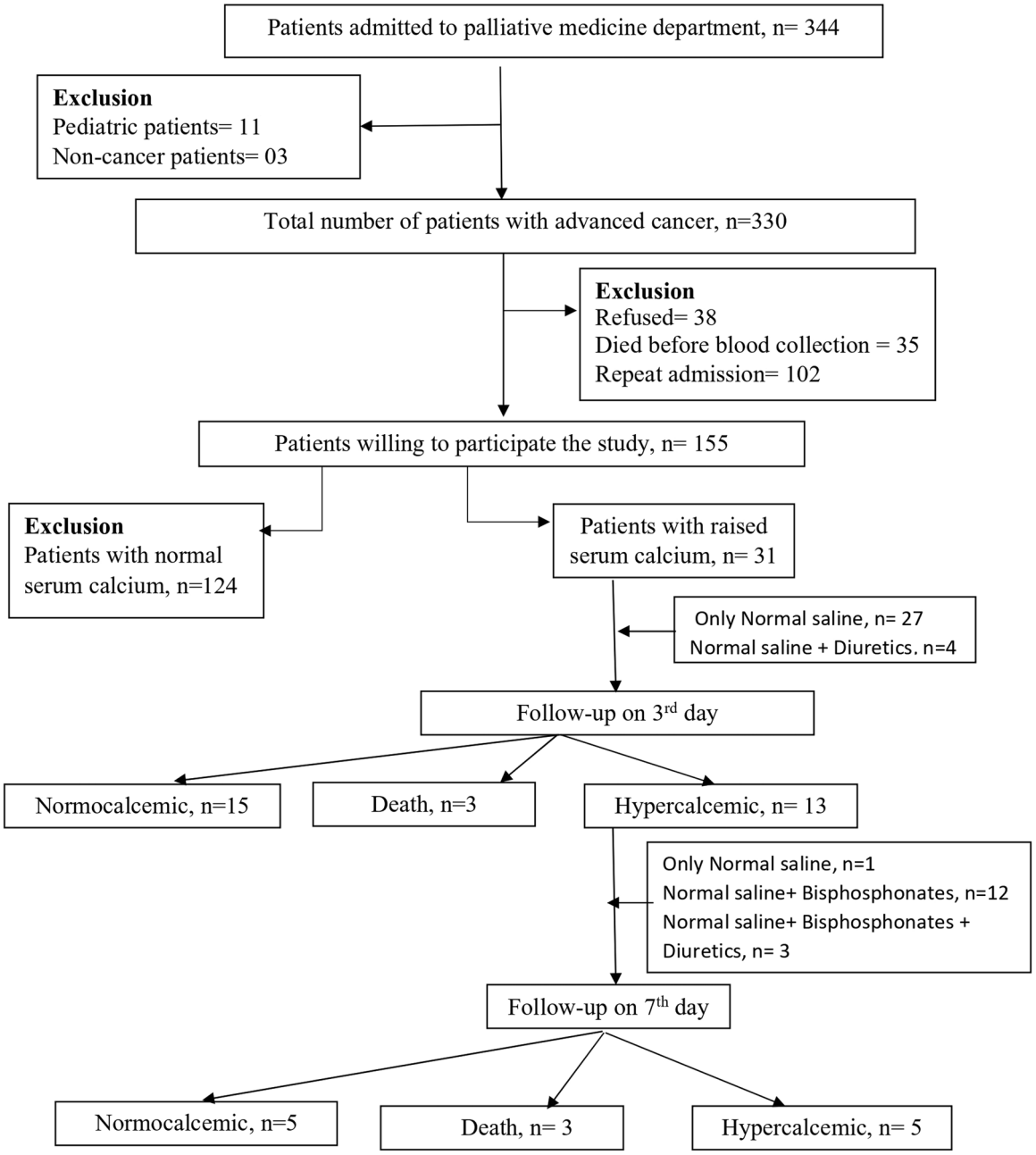

FIGURE 1 | Recruitment procedure and treatment outcome of patients with hypercalcemia of malignancy.

diuretics, bisphosphonate) deemed appropriate by the palliative care team. Those patients were monitored and followed up on the 7th day. Serum calcium and albumin levels were also checked on the same day. Reports were collected and noted in the data collection sheet and rechecked by the research team.

2.5 | Data Analysis

All statistical analyses were performed using SPSS version 26. Continuous variables like age, monthly income, duration of the disease, biochemical, and hematological data were presented by mean, SD, median, and range. Qualitative variables like gender, cancer type, staging, treatment status, HCM categories, signs, and symptoms were expressed as frequency, percentage, and graphs. Paired *t*-test was done to see the treatment response of the hypercalcemic patients. Chi-square test, Fisher's exact test, and unpaired *t*-test were done to see the changes in clinical findings following treatment. All of the means were calculated at a 95% confidence interval, and p value < 0.05 was considered as the level of statistical significance.

2.6 | Ethical Considerations

The ethical approval (approval no: BSMMU/2023/8891, date: 15/06/2023) was obtained from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University, Bangladesh. Written informed consent was taken from all the eligible patients and/or their caregivers.

3 | Results

Among the 31 participants, 67.7% participants were male, and 32.2% participants were female, with an average age of 52.65 ± 13.88 years. A majority (70.9%) of the patients were admitted to the palliative medicine department within 6 months of diagnosis. Most patients were at stage-IV and bed-bound (74.1%) (Table 1).

We found lethargy (100%) to be the most common symptom among the hypercalcemic patients, followed by constipation (67.7%), anorexia (64.5%), nausea (61.3%), abdominal pain (45.2%), vomiting (41.9%), polydipsia (38.7%), polyuria (33.5%). Signs of some dehydration were observed in 70.9% of patients, with 25.8% were severely dehydrated. Their mean Glasgow Coma Scale (GCS) score was 13.54 ± 2.52 (Table 2).

On the day of admission, 16 (51.6%) patients had mild HCM, 8 (25.8%) had severe HCM, and 7 (22.6%) had moderate HCM. Normal saline was administered to all 31 patients. Diuretics were administered to 4 (12.9%) patients along with normal saline to prevent volume overload due to their impaired cardiac status (Table 3 and Figure 1).

TABLE 1 | Distribution of study population according to socio-demographic and disease related characteristics ($n = 31$).

Variables	Frequency	Percentage
Age (in years)		
18–40	4	12.9
41–65	21	67.7
Above 65	6	19.3
Mean ± SD (years)	52.65 ± 13.88	
Sex		
Male	21	67.7
Female	10	32.2
Primary diagnosis		
Gastrointestinal system	7	22.5
Respiratory system	4	12.9
Head and neck	3	9.6
Others	17	54.8
Stage of cancer		
Stage-III	8	25.8
Stage-IV	23	74.1
Duration since diagnosis		
Upto 6 months	22	70.9
7–14 months	3	9.6
Above 15 months	6	19.3
ECOG performance status		
Confined to bed more than 50% of waking hours	8	25.8
Completely bedbound	23	74.1

During the first follow-up after 3 days, the mean serum calcium level decreased significantly from 12.43 ± 1.96 to 10.82 ± 2.07 following 3 days of normal saline administration. After 3 days of rehydration therapy, 13 (42%) patients remained hypercalcemic, 15 (48%) improved, and 3 (10%) patient died (Table 4 and Figure 1).

Lethargy persisted in the majority of patients even after initial treatment, possibly due to their primary disease. However, symptoms such as confusion, seizures, abdominal pain, drowsiness, and vomiting resolved in those who became normocalcemic, while these symptoms persisted in remaining

TABLE 2 | Distribution of the study population according to clinical presentation on admission ($n = 31$).

Symptoms[a]	Frequency	Percentage
Lethargy	31	100
Confusion	10	32.3
Polyuria	11	35.4
Polydypsia	12	38.7
Nausea	19	61.3
Puritus	1	3.2
Vomiting	13	41.9
Abdominal pain	14	45.2
Constipation	21	67.7
Drowsiness	10	32.3
Anorexia	20	64.5
Signs[a]		
Some dehydration	22	70.9
Severe dehydration	8	25.8
Urine volume (L/day)		
0.5–1	9	29.0
1–3	20	64.5
> 3	2	6.4
GCS score		
Mean ± SD	13.54 ± 2.52	

[a]Multiple response.

TABLE 3 | Distribution of the study population according to severity of hypercalcemia and received treatment on 1st day ($n = 31$).

Variables	Frequency	Percentage
Severity of hypercalcemia		
Mild hypercalcemia	16	51.6
Moderate hypercalcemia	7	22.6
Severe hypercalcemia	8	25.8
Treatment received[a]		
Normal saline	31	100
Diuretics (Furosemide)	4	12.9

[a]Multiple responses.

TABLE 4 | Treatment response of hypercalcemia on 1st follow-up ($n = 31$).

Serum calcium level before treatment Mean ± SD	Serum calcium level after treatment with normal saline (at 3rd day) Mean ± SD	*t*-value	*p* value
12.43 ± 1.96	10.82 ± 2.07	6.158	< 0.001[a,b]
Hypercalcemia status	**Frequency**		**Percentage**
Improved (normocalcemia)	15		48
Death	3		10
Static (hypercalcemia)	13		42

[a]*p* Value reached through paired *t*-test.
[b]Significant.

TABLE 5 | Changes in the clinical presentation of hypercalcemia on the 1st follow-up ($n = 28$).

Symptoms[a]	Static (hypercalcemia) ($n = 13$) Frequency (%)	Improved (normocalcemia) ($n = 15$) Frequency (%)	*p* value
Lethargy	13 (100)	5 (33.3)	< 0.033[d]
Confusion	5 (38.5)	0 (0)	< 0.013[b,d]
Seizure	1 (7.6)	0 (0)	> 0.99[b,e]
Polydipsia	2 (15.4)	1 (6.6)	0.583[b,e]
Polyuria	5 (38.5)	4 (26.6)	0.689[b,e]
Nausea	3 (23.1)	2 (13.3)	0.629[b,e]
Anorexia	6 (46.2)	12 (80)	0.114[b,e]
Vomiting	3 (23.1)	0 (0)	0.087[b,e]
Abdominal pain	1 (7.6)	0 (0)	0.464[b,e]
Constipation	6 (46.2)	3 (20)	0.228[b,e]
Drowsiness	5 (38.5)	0 (0)	0.013[b,d]
Signs[a]			
Some dehydration	8 (61.5)	0 (0)	< 0.001[b,d]
Severe dehydration	2 (15.4)	0 (0)	0.206[b,e]
GCS score			
Mean ± SD	12.23 ± 3.70	14.93 ± 0.25	0.009[c,d]

Note: Data presented as frequency and percentage over rows. Mean ± SD presented over rows.
[a]Multiple response. Only 'yes' responses are shown
[b]*p* Value reached through Fisher's exact test was taken where the expected value was < 5 in ≥ 20% cells.
[c]Unpaired *t*-test was used for normally distributed continuous variables.
[d]Significant.
[e]Nonsignificant.

hypercalcemic patients. Majority of the hypercalcemic patients remained dehydrated, while normocalcemic patients improved. These patients also had a significantly lower mean GCS score (12.23 ± 3.70) compared to those who improved (14.93 ± 0.25) (Table 5).

Among the remaining hypercalcemic patients, 6 (46.2%) had mild HCM, 5 (38.5%) had moderate HCM, and 2 (15.4%) had severe HCM. Normal Saline was administered in all patients. Bisphosphonate (92.3%) and Diuretics (23.1%) were used in patients along with normal saline (Table 6 and Figure 1).

A substantial decrease was observed in the mean serum calcium level, from 12.66 ± 1.91 to 10.27 ± 0.75, after treatment with normal saline and bisphosphonates, with a highly significant *p* value of < 0.001. After both rehydration and bisphosphonate therapy, 5 (38.5%) participants remained hypercalcemic, 5 (38.5%) patients improved, and 3 (23%) died on the 7th day of follow-up. All remaining patients had mild HCM (Table 7 and Figure 1).

After both rehydration and bisphosphonate therapy, symptoms like confusion, drowsiness, and vomiting completely resolved in patients who improved. However, lethargy, nausea, and anorexia persisted, possibly due to the underlying disease condition. Their GCS level also improved. Dehydration completely resolved in patients who improved, while hypercalcemic patients remained mildly dehydrated (Table 8).

TABLE 6 | Distribution of the study population according to severity of hypercalcemia and received treatment on 3rd day onwards ($n = 13$).

Variables	Frequency	Percentage
Severity of hypercalcemia		
Mild hypercalcemia	6	46.2
Moderate hypercalcemia	5	38.5
Severe hypercalcemia	2	15.4
Treatment received[a]		
Normal saline	13	100
Bisphosphonate (zoledronic acid)	12	92.3
Diuretics (furosemide)	3	23.1

[a]Multiple responses.

4 | Discussion

HCM is a palliative care emergency. In this study, we explored the clinical presentations and treatment outcomes of HCM among this population.

We found that normal saline had been administered to 100% of patients. Intravenous fluids are widely accepted as a first-line treatment for all types of hypercalcemia, including hypercalcemia of malignancy. Patients with HCM typically present with dehydration secondary to multiple underlying factors, including anorexia, nausea, and vomiting, which are common clinical manifestations of HCM [11]. Aggressive rehydration, generally with 0.9% sodium chloride solution (normal saline), is commonly recommended for the treatment of HCM as supported by numerous studies and several meta-analyses [11–13]. We followed the same protocol recommended by these studies.

TABLE 7 | Treatment response of hypercalcemia on 2nd follow-up (n = 13).

Serum calcium level on 3rd day (treatment with normal saline) Mean ± SD	Serum calcium level after treatment with normal saline and bisphosphonate Mean ± SD	*t*-value	*p* value
12.66 ± 1.91	10.27 ± 0.75	4.33	0.001[a,b]
Hypercalcemia status	**Frequency**		**Percentage**
Improved (normocalcemia)	5		38.5
Death	3		23
Static (hypercalcemia)	5		38.5

[a]*p* value reached through paired *t*-test.
[b]Significant.

TABLE 8 | Changes in the clinical presentation of hypercalcemia on the 2nd follow-up ($n = 10$).

Symptoms[a]	Static (hypercalcemia) ($n = 5$) Frequency (%)	Improved (normocalcemia) ($n = 5$) Frequency (%)	*p* value
Lethargy	2 (40)	1 (20)	0.129[b,d]
Confusion	2 (40)	0 (0)	0.429[b,d]
Nausea	0 (0)	1 (20)	> 0.992[b,d]
Anorexia	1 (20)	3 (60)	0.486[b,d]
Vomiting	1 (20)	0 (0)	> 0.995[b,d]
Drowsiness	2 (40)	0 (0)	0.429[b,d]
Signs[a]			
Some dehydration	3 (60)	0 (0)	0.143[b,d]
Urine volume (L)			
1–3	1 (40)	0 (0)	
> 3	3 (60)	4 (80)	> 0.998[b,d]
GCS score			
Mean ± SD	10 ± 4.96	14.75 ± 0.50	0.106[c,d]

Note: Data presented as frequency and percentage over rows. Mean ± SD presented over rows.
[a]Multiple response. Only 'yes' answers are shown.
[b]*p* value reached through Fisher's exact test was taken where the expected value was < 5 in ≥ 20% cells.
[c]Unpaired *t*-test was used for normally distributed continuous variables.
[d]Nonsignificant.

We also found that rehydration therapy significantly reduced serum calcium levels by the third day of follow-up, demonstrating a notable improvement within the observed timeframe. Our findings align with those of a study conducted in the United Kingdom, where rehydration therapy resulted in significant improvement among the majority of hypercalcemic patients [14].

Bisphosphonates (92.3%) were given to patients who remained hypercalcemic even after rehydration therapy in our study setup. We observed a significant reduction in serum calcium levels following bisphosphonate administration in the majority (97.2%) of patients. Bisphosphonates have been shown to be safe and effective for treating HCM, as supported by a meta-analysis [15]. Our findings also aligns with a systematic review by Saunders et al. [16], which concluded that more than 70% of hypercalcemic patients showed improvement after bisphosphonate therapy [16].

In our study, lethargy (100%) was the most common symptom, followed by gastrointestinal and neurological symptoms. Our findings align with a meta-analysis by Santarpia et al. [17], where neurological symptoms were identified as a major presentation among hypercalcemic patients. Several systematic reviews have also reported psychiatric and renal symptoms to be more prevalent among HCM patients [3]. Nonspecific symptoms such as malaise and fatigue were also commonly observed among hypercalcemic patients, which is consistent with our findings [18]. However, symptom manifestation mostly depends on the severity of HCM [17]. Mild HCM may be asymptomatic or present with nonspecific symptoms, while severe HCM can be associated with a variety of life-threatening symptoms [19, 20]. However, we found that these symptoms (pain, nausea, anorexia, vomiting, and confusion) improved or disappeared after the normalization of serum calcium, which coincides with findings from a study conducted in France [21]. Our findings support the argument for the benefits of treating HCM in the terminal phase. We observe that effective, well-tolerated therapies can provide symptom relief and, therefore, increase patient comfort [8].

Overall improvement was observed in 64.5% of hypercalcemic patients, while 16.1% remained stable, and 19.4% died during the period of our study, reflecting the effectiveness of the provided medical interventions. Our improvement rate was comparable to that of American cancer patients with HCM (69.1%). However, our mortality rate was lower compared to a study conducted among British cancer patients, where the mortality rate was relatively higher (36.4%) among hypercalcemic patients [22]. Similarly, another study found that, advanced cancer patients with HCM also had a significantly higher mortality rate (39.1%), and the mortality rate increased with the severity of HCM [23]. The in-hospital mortality rate of patients with advanced cancer (19.4%) in our study aligns with the findings from Mao et al. [24], whereas the study by Diao et al. [25] reported a higher in-hospital mortality rate of 29.4%, exceeding our findings.

Based on our findings, we support the benefits of treating hypercalcemia of malignancy. In our study, both doctors and patients reported satisfactory outcomes from HCM treatment, even at the terminal stage. Our findings also align with those of Bassatne et al. [8], where all doctors agreed that treating HCM enhances quality of life by reducing symptom burden and hospital stay, and, in some cases, even decreases mortality. However, that study also emphasized that treatment options must be carefully considered to balance the risks and benefits [8].

4.1 | Limitations

Our study had several limitations. First, it was conducted in only one center with a small sample size, so our findings cannot be generalized. Additionally, we did not perform costly investigations such as measuring levels of PTH, PTHrP, or Vitamin D, which are also common mediators of HCM. We did not conduct ECGs to evaluate cardiac manifestations of HCM or utilize costly imaging modalities like CT scans, MRI, or PET scans to exclude other potential causes and manifestations of HCM, which could have contributed to a similar clinical presentation. The high variability in the data due to age, gender, and type of malignancy is a notable factor. The age range starting at 18 introduces significant variability, as the pathogenesis of malignancy may differ with increasing age. Similarly, gender can influence the development and treatment of HCM. To reduce this limitation, further study with a larger sample size would be beneficial.

5 | Conclusion

Malignant hypercalcemia, a potentially fatal complication of advanced malignancy, often remains undiagnosed and undertreated. Early detection and treatment are crucial for improving patient outcomes and facilitating earlier discharge from the hospital. Cost-effective treatments, such as rehydration therapy, can benefit approximately 50% of hypercalcemic patients. For others, more expensive treatments like bisphosphonates may be required to lower serum calcium levels, though the number of such cases is relatively low. It is essential for palliative care providers to identify HCM and develop a comprehensive care plan that includes regular monitoring and management of calcium levels. This approach optimizes treatment outcomes, alleviates suffering, and enhances quality of life, ensuring patients receive the most effective and personalized care possible.

Author Contributions

Rafsana Rouf: conceptualization, investigation, funding acquisition, writing–original draft, methodology, validation, visualization, writing–review and editing, software, formal analysis, project administration, data curation, supervision, resources. **A. K. M. Motiur Rahman Bhuiyan:** conceptualization, methodology, writing–original draft, writing–review and editing, funding acquisition, validation, visualization, supervision, project administration. **Afroja Alam:** conceptualization, writing–original draft, writing–review and editing, methodology, validation, supervision. **Mostofa Kamal Chowdhury:** conceptualization, investigation, writing–original draft, writing–review and editing, methodology, validation, visualization, formal analysis, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data relevant to the study are available upon request to the corresponding author.

Transparency Statement

The lead author Dr. Rafsana Rouf affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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