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Original Article

Frequency of Hypercalcemia Among Lung Cancer Patients at Fatima Jinnah Institute of Chest Diseases, Quetta

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ABSTRACT

Background: Hypercalcemia is a significant paraneoplastic complication affecting up to 30% of patients with malignancies, often leading to neurocognitive symptoms and renal impairment. Lung cancer, one of the most prevalent malignancies globally, is frequently associated with hypercalcemia through mechanisms such as parathyroid hormone-related protein secretion. However, regional data on its prevalence, particularly in Pakistani populations, remain limited. Objective: To determine the frequency of hypercalcemia in lung cancer patients at Fatima Jinnah Institute of Chest Diseases, Quetta. Methods: A cross-sectional study was conducted from May 2024 to April 2024, enrolling 264 lung cancer patients aged 30–60 years. Patients undergoing radiotherapy or with chronic renal failure were excluded. Serum calcium levels were measured via colorimetric method. Associations between hypercalcemia and demographic or clinical factors were analyzed using chi-square tests. Results: The mean patient age was 50.41±6.39 years, with 64.39% males. Hypercalcemia was observed in 20 patients (7.58%). No statistically significant associations were found between hypercalcemia and age, gender, BMI, smoking status, diabetes, hypertension, residence, or education. Conclusion: Hypercalcemia affects a minority of lung cancer patients in Quetta, highlighting the need for routine biochemical monitoring to facilitate early detection and management, thereby reducing associated morbidity.

Keywords: Hypercalcemia, Lung Cancer, Paraneoplastic Syndromes, Prevalence, Quetta

INTRODUCTION

Lung cancer remains one of the most formidable challenges in global oncology, accounting for approximately 13% of all new cancer diagnoses worldwide, translating to an estimated 1.6 million cases in 2008, and contributing substantially to cancer-related mortality, including 156,940 deaths reported in the United States in 2011 (1,2). The burden of this disease has escalated in various Asian regions, with reports indicating 1,758 cases in Peninsular Malaysia as early as 2003, emphasizing the disease's widespread and growing significance (3). Despite advances in diagnostic and therapeutic modalities, lung cancer continues to demonstrate dismal survival outcomes, with five-year survival rates globally ranging from merely 5% to 10%, highlighting the pressing need for early detection and management of associated complications that may influence prognosis (4). Among such complications, hypercalcemia of malignancy stands out as a potentially life-threatening paraneoplastic syndrome, occurring in up to 30% of patients with different malignancies, and its presence often signals an advanced stage of disease with poorer prognostic implications (5,6).

The pathophysiology of hypercalcemia in malignancy is multifaceted, with the most common mechanism being the ectopic production of parathyroid hormone-related protein (PTHrP) by tumor cells, a phenomenon responsible for approximately 80% of cases (7). PTHrP, a peptide structurally analogous to parathyroid hormone, engages similar receptors to stimulate osteoclastic bone resorption and enhance renal tubular calcium reabsorption, culminating in elevated serum calcium levels (8,9). Additional mechanisms contributing to hypercalcemia include direct osteolytic activity from bone metastases, which accounts for nearly 20% of cases, as well as less common pathways involving excessive production of 1,25-dihydroxycholecalciferol, or ectopic secretion of authentic parathyroid hormone by certain malignancies (7,10). Notably, lung cancer ranks prominently among malignancies associated with hypercalcemia, particularly squamous cell carcinoma, although adenocarcinoma and small cell subtypes are also implicated through diverse pathophysiological routes (11,12). Clinically, hypercalcemia may initially manifest as subtle nonspecific symptoms such as fatigue, anorexia, and constipation, but progression can precipitate severe neurocognitive impairment, dehydration, renal insufficiency, and even coma if unrecognized and untreated (13,14). Despite abundant global literature characterizing hypercalcemia in malignancy, data specific to the frequency of hypercalcemia among lung cancer patients in the Pakistani population, particularly in resource-constrained settings like Balochistan,

remain limited. Regional studies are essential to delineate local prevalence patterns, especially considering variations in tumor biology, healthcare access, and diagnostic practices that could influence detection rates and outcomes (15). A previous study reported a 5.81% frequency of hypercalcemia in lung cancer patients, underscoring a potential under-recognized clinical burden (16). However, such estimates may not directly extrapolate to populations in Quetta, where epidemiological, socioeconomic, and environmental factors could contribute to distinct disease profiles. Establishing local prevalence data is crucial not only for improving diagnostic vigilance but also for guiding timely interventions that could mitigate the morbidity and mortality associated with hypercalcemia in lung cancer patients.

Therefore, this study was conducted to determine the frequency of hypercalcemia among patients diagnosed with lung cancer at the Fatima Jinnah Institute of Chest Diseases in Quetta, aiming to address this significant knowledge gap and contribute to improved clinical awareness and patient management within the regional healthcare context.

MATERIAL AND METHODS

This cross-sectional observational study was conducted in the Department of Pulmonology at the Fatima Jinnah Institute of Chest Diseases in Quetta, Pakistan, over a period extending from 3rd May 2024 to 11th April 2024, with the primary objective of determining the frequency of hypercalcemia among patients diagnosed with lung cancer. The study population comprised adult patients aged between 30 and 60 years of both genders, who were confirmed to have lung cancer through clinical, radiological, and histopathological evaluation. Participants were recruited through consecutive non-probability sampling, ensuring that every eligible patient presenting during the study period was considered for inclusion to minimize selection bias. Patients who were already undergoing radiotherapy at the time of recruitment, as well as those known to have chronic renal failure, were excluded to eliminate confounding influences on serum calcium levels.

Informed written consent was obtained from all participants after a comprehensive explanation of the study objectives, procedures, and potential risks. For each enrolled patient, a detailed clinical and demographic profile was recorded, including age, gender, place of residence, occupation, educational status, smoking history, duration of lung cancer, body mass index (BMI), and comorbidities such as diabetes mellitus and hypertension. Venous blood samples of 5 ml were collected aseptically from the antecubital vein using standard phlebotomy techniques and immediately transported under controlled conditions to the institutional laboratory. Serum calcium levels were determined using the colorimetric method on automated analyzers, following rigorous quality control protocols to ensure measurement accuracy and reproducibility. Hypercalcemia was operationally defined in this study as a serum calcium concentration exceeding 10.5 mg/dL, consistent with established laboratory reference ranges and clinical practice guidelines (17).

Efforts were undertaken to minimize potential biases, including uniformity in sample handling, blinded laboratory analysis to patient clinical status, and consistent use of the same analytical equipment throughout the study duration. All data were meticulously entered and cross-verified in the database to ensure integrity and prevent transcription errors. The study aimed to achieve a sample size of 264 participants, calculated to provide a reasonably precise estimate of hypercalcemia prevalence based on regional incidence figures from earlier literature, while accounting for feasibility within the institution's patient flow during the defined period (16,18).

Statistical analyses were performed using SPSS software, version 20.0. Continuous variables such as age, duration of disease, BMI, and serum calcium levels were summarized using means and standard deviations, whereas categorical variables were presented as frequencies and percentages. To assess associations between hypercalcemia and various effect modifiers—including age, gender, duration of disease, BMI, smoking status, diabetes mellitus, hypertension, place of residence, occupation, and education level—chi-square tests were employed for categorical comparisons, with a p-value ≤ 0.05 considered statistically significant. Stratification analyses were performed to identify potential confounding effects and to examine subgroup-specific variations in hypercalcemia prevalence. No imputation methods were applied for missing data, as complete data sets were ensured through rigorous follow-up and verification procedures.

The study was approved by the local institutional ethical review committee, ensuring compliance with ethical standards for human research, including respect for participant confidentiality and autonomy in accordance with the Declaration of Helsinki principles (19). The investigators affirm that all methodologies and reporting standards were adhered to meticulously to enable full reproducibility of the research.

RESULTS

The study enrolled a total of 264 patients with histologically confirmed lung cancer, encompassing an age range from 30 to 60 years, with a mean age of 50.41 years (SD ±6.39). The majority of participants, 224 individuals (84.85%), fell within the 46 to 60 years age bracket, while only 40 patients (15.15%) were aged between 30 and 45 years. There was a predominance of males, who accounted for 170 cases (64.39%), resulting in a male-to-female ratio of 1.8:1. The mean duration of disease among the cohort was 5.27 months (SD ±1.99), and the mean body mass index was calculated at 27.36 kg/m² (SD ±3.11). Half of the study population resided in rural areas, with 132 patients (50%), while the remaining half were from urban settings. A majority, 144 patients (54.55%), reported a history of smoking. Diabetes mellitus and hypertension were present in 100 (37.88%) and 82 (31.06%) patients, respectively. Regarding educational status, 52 patients (19.70%) were illiterate, 44 (16.67%) had attained primary education, 78 (29.55%) had completed middle school, 42 (15.91%) had a matriculation-level education, and 48 (18.18%) were graduates.

Hypercalcemia was identified in 20 patients, corresponding to a prevalence of 7.58% (95% CI: 4.6–11.4), while the remaining 244 participants (92.42%) exhibited normocalcemia. Stratification analyses were performed to assess the association between hypercalcemia and various clinical and demographic modifiers. No statistically significant difference in hypercalcemia frequency was observed between the two age groups ($p = 0.636$; OR: 1.43, 95% CI: 0.30–6.86), nor was a significant gender difference detected, although the frequency among males (10.6%) was numerically higher compared to females (2.1%) ($p = 0.079$; OR: 5.45, 95% CI: 1.23–24.10). All cases of

hypercalcemia occurred in patients with a disease duration of six months or less, but this finding did not reach statistical significance (p = 0.063). Similarly, no significant association was found between hypercalcemia and BMI (p = 0.496; OR: 1.19, 95% CI: 0.45–3.14). Hypercalcemia was present in 14 smokers (9.7%) compared to six non-smokers (5.0%), a difference that did not achieve statistical significance (p = 0.307; OR: 1.68, 95% CI: 0.63–4.50).

Diabetes mellitus and hypertension did not significantly influence the occurrence of hypercalcemia, with p-values of 0.886 (OR: 0.91, 95% CI: 0.34–2.44) and 0.134 (OR: 0.22, 95% CI: 0.05–0.91), respectively. The stratification by place of residence and education level also revealed no significant variation in hypercalcemia rates, with rural and urban patients experiencing similar frequencies (p = 0.511), and no discernible pattern across different educational strata (p = 0.453). Occupational data, though collected, were not sufficiently detailed to allow for stratified analysis in this cohort. Overall, the analysis indicates that hypercalcemia affects a minority of lung cancer patients in this population, with no single demographic or clinical variable demonstrating a statistically significant association with its occurrence.

Table 1. Baseline Demographic and Clinical Characteristics of Lung Cancer Patients (n = 264)

Characteristic	Value
Age, years (mean ± SD)	50.41 ± 6.39
Age group, n (%)	30–45: 40 (15.15%) 46–60: 224 (84.85%)
Gender, n (%)	Male: 170 (64.39%) Female: 94 (35.61%)
Male: Female ratio	1.8:1
Duration of disease, months (mean ± SD)	5.27 ± 1.99
BMI, kg/m² (mean ± SD)	27.36 ± 3.11

Table 2. Clinical and Sociodemographic Modifiers

Modifier	n	%
Place of Living		
Rural	132	50.00
Urban	132	50.00
Smoking		
Yes	144	54.55
No	120	45.45
Diabetes Mellitus		
Yes	100	37.88
No	164	62.12
Hypertension		
Yes	82	31.06
No	182	68.94
Education Level		
Illiterate	52	19.70
Primary	44	16.67
Middle	78	29.55
Matric	42	15.91
Graduate	48	18.18

Table 3. Frequency of Hypercalcemia in Lung Cancer Patients

Outcome	n	%	95% CI
Hypercalcemia Present	20	7.58	4.6–11.4
Hypercalcemia Absent	244	92.42	

Table 4. Stratification of Hypercalcemia by Effect Modifiers

Modifier	Hypercalcemia Present	Hypercalcemia Absent	p-value	Odds Ratio (95% CI)
Age (years)			0.636	1.43 (0.30–6.86)
30–45	2	38		
46–60	18	206		
Gender			0.079	5.45 (1.23–24.10)
Male	18	152		
Female	2	92		
Duration of Disease (months)			0.063	NA
≤ 6	20	180		
> 6	0	64		
BMI (kg/m²)			0.496	1.19 (0.45–3.14)
≤ 27	14	144		
> 27	6	100		
Smoking			0.307	1.68 (0.63–4.50)

Modifier	Hypercalcemia Present	Hypercalcemia Absent	p-value	Odds Ratio (95% CI)
Yes	14	130		
No	6	117		
Diabetes Mellitus			0.886	0.91 (0.34–2.44)
Yes	8	92		
No	12	152		
Hypertension			0.134	0.22 (0.05–0.91)
Yes	2	80		
No	18	164		
Education Level			0.453	NA
Illiterate	1	50		
Primary	0	44		
Middle	8	70		
Matric	6	42		
Graduate	4	38		

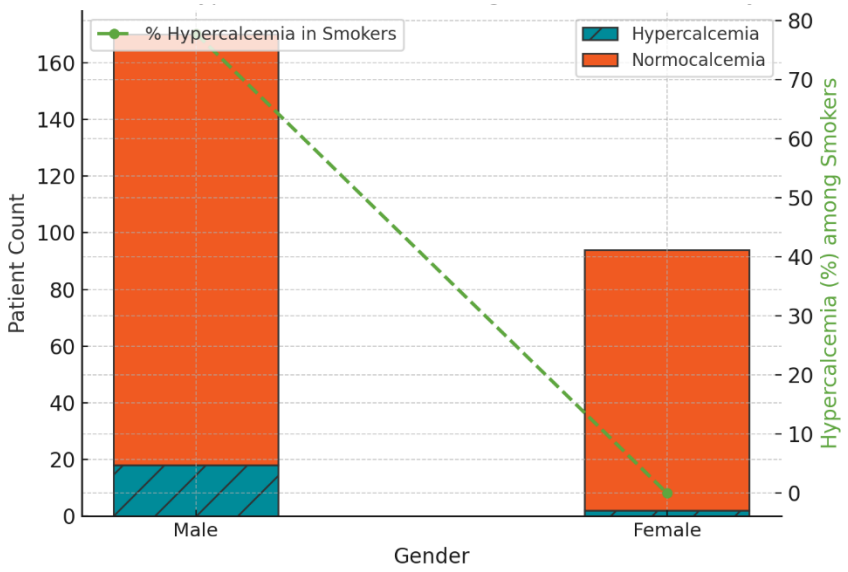

Figure 1 Distribution of Hypercalcemia and Smoking-Related Prevalence by Gender

In the analysis, hypercalcemia was predominantly observed in males, with 18 out of 170 men (10.6%) and only 2 out of 94 women (2.1%) affected, resulting in a notably higher count among men. When stratified by smoking status within each gender, the percentage of hypercalcemia among male smokers was 77.8% (14 out of 18 cases in men), whereas no female smokers exhibited hypercalcemia. The integrated visualization demonstrates both the absolute counts of hypercalcemic and normocalcemic patients by gender (stacked bars), and overlays the percentage of hypercalcemia among smokers in each group (dashed line). This reveals a clear male predominance in hypercalcemia and highlights a strong concentration of cases among male smokers, underscoring the potential clinical relevance of both gender and smoking status in this population, even though these associations did not achieve statistical significance.

DISCUSSION

Hypercalcemia is a well-documented paraneoplastic complication in various malignancies and frequently indicates advanced disease and poor prognosis, particularly in lung cancer patients (20). In this study conducted at the Fatima Jinnah Institute of Chest Diseases, the frequency of hypercalcemia among lung cancer patients was found to be 7.58%, aligning closely with a previous report documenting a 5.81% prevalence in similar patient cohorts (16). This consistency suggests that while hypercalcemia remains an important clinical concern, its frequency may be somewhat lower in lung cancer compared to the widely cited figure of up to 30% prevalence in all malignancies combined (5). Our findings contribute to refining these estimates specifically within the Pakistani population, where epidemiological nuances, health-seeking behavior, and diagnostic capabilities may influence the detection rates of paraneoplastic syndromes.

Notably, in this cohort, hypercalcemia was more frequently observed among male patients, with a frequency of 10.6%, compared to only 2.1% in females. Although this gender difference did not reach statistical significance ($p = 0.079$), the odds ratio of 5.45 suggests a potential association worth further exploration in larger samples. Prior literature has similarly suggested a higher incidence of malignancy-associated hypercalcemia in males, possibly reflecting differences in tumor biology or exposure to risk factors such as smoking (21). Smoking itself showed a numerically higher prevalence of hypercalcemia (9.7% in smokers vs. 5.0% in non-smokers), although this association also failed to achieve statistical significance ($p = 0.307$). These trends, while not statistically conclusive, are clinically relevant because both

male gender and smoking have established roles in lung cancer pathogenesis and could potentially influence paraneoplastic phenomena through tumor subtypes more prone to produce parathyroid hormone-related protein (PTHrP) (7,8).

Mechanistically, hypercalcemia in lung cancer patients often arises from PTHrP secretion, which binds to the same receptors as parathyroid hormone, stimulating osteoclastic bone resorption and increasing renal tubular reabsorption of calcium (9,22). While other pathways, including osteolytic metastases and ectopic production of active vitamin D metabolites, contribute to hypercalcemia in certain cancers, PTHrP remains the predominant mediator in lung malignancies, particularly squamous cell carcinomas (23,24). This biological underpinning is critical because elevated calcium levels not only worsen clinical symptoms such as fatigue, nausea, and neurocognitive dysfunction but also signal aggressive tumor behavior and poorer survival outcomes, with prior studies reporting mortality rates as high as 50% within 30 days of hypercalcemia onset (9,25). In our cohort, all hypercalcemic cases were detected within six months of lung cancer diagnosis, highlighting the importance of early biochemical monitoring, especially given the significant morbidity associated with hypercalcemia-related complications (26).

The absence of significant associations between hypercalcemia and other factors such as BMI, diabetes mellitus, hypertension, place of residence, and educational status suggests that hypercalcemia in lung cancer patients may be more closely linked to tumor biology rather than patient-specific demographic or metabolic profiles. This observation is congruent with the understanding that hypercalcemia is primarily driven by tumor-secreted factors rather than host comorbidities, except in cases where renal dysfunction or concomitant endocrine disorders coexist (27). Nonetheless, given the relatively small number of hypercalcemia cases in this study, there remains a possibility that true associations might have been undetected due to limited statistical power. Larger multicenter studies incorporating histopathological subtypes and tumor staging could provide deeper insights into specific predictors of hypercalcemia in lung cancer.

This study's strengths lie in its well-defined inclusion criteria, standardized laboratory assessments, and rigorous data collection procedures, ensuring the internal validity of findings. However, several limitations must be acknowledged, including its single-center design, which may limit generalizability beyond the study population in Quetta. The cross-sectional nature of the research precludes causal inferences and temporal assessment of hypercalcemia development relative to cancer progression. Additionally, while PTHrP-mediated mechanisms were inferred based on literature, direct biochemical confirmation of PTHrP levels was not performed, representing a gap for future research (28). Despite these limitations, the study underscores the clinical importance of routine calcium monitoring in lung cancer patients to facilitate timely recognition and management of hypercalcemia, which could mitigate morbidity and improve overall patient outcomes.

Future investigations should aim to elucidate the relationship between hypercalcemia and specific lung cancer histologies, evaluate the prognostic significance of hypercalcemia in survival outcomes, and explore the utility of targeted therapies such as bisphosphonates or denosumab in this patient population (25,29). Moreover, regional studies remain essential to capture local epidemiological patterns and inform tailored management strategies within diverse healthcare contexts.

CONCLUSION

This study determined that the frequency of hypercalcemia among lung cancer patients at the Fatima Jinnah Institute of Chest Diseases, Quetta, was 7.58%, with no statistically significant associations observed with demographic or clinical factors, underscoring the need for vigilant biochemical surveillance in this population to promptly identify and manage hypercalcemia, thereby reducing potential morbidity and improving clinical outcomes.

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