Original Article

Prevalence and Etiological Profile of Hypercalcemia in Hospitalized Adult Patients and Association with Mortality

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Abstract

Background: The etiology of hypercalcemia varies according to the clinical setting. Hitherto, data on the prevalence and profile of hypercalcemia in hospitalized Asian–Indian patients are limited. Hence, we conducted a prospective observational study to determine the prevalence and etiological profile of hypercalcemia in hospitalized Asian–Indian patients and its association with 6-month mortality. **Materials and Methods:** We conducted a prospective observational study wherein all the patients (aged >12 years) admitted to the general medicine wards of a tertiary care hospital in North India between January 1, 2016, and June 30, 2017, were screened. Finally, patients with sustained hypercalcemia (defined as corrected serum total calcium ≥10.4 mg/dl documented twice at least 24 h apart) were included in this study. These patients were followed up throughout the hospital course and thereafter till 6 months from the date of discharge. **Results:** Out of 9902 patients, 150 patients had sustained hypercalcemia (prevalence 1.5%). The most common cause of hypercalcemia was malignancy (41.3%), followed by primary hyperparathyroidism (PHPT, 32.7%). Vitamin D intoxication was responsible for hypercalcemia in 8.7% of patients; 2.7% of patients had hypercalcemia of advanced chronic liver disease. Nevertheless, a definite etiology could not be identified in 7.3% of the patients with hypercalcemia. At the end of 6 months of follow-up, the cumulative mortality rate was 28%. Underlying malignancy and higher calcium levels were the significant determinants of mortality. **Conclusions:** The prevalence of hypercalcemia in Asian–Indian patients admitted to a tertiary care hospital was 1.5%. The most common etiology was malignancy, followed by PHPT.

Keywords: Hypercalcemia, malignancy, mortality, primary hyperparathyroidism

Introduction

Hypercalcemia is a frequent electrolyte abnormality in out and inpatients and the emergency department. Dysregulation of calcium balance is relatively common and is often associated with significant morbidity and mortality. Hypercalcemia is often a surrogate marker of underlying pathology; hence, it needs detailed evaluation to ascertain the etiology. Delineating the exact etiology is essential for the early institution of appropriate treatment. Primary hyperparathyroidism (PHPT) and malignancy (including hematological malignancies) account for more than 90% of the cases of hypercalcemia. More than 90% of all causes of hypercalcemia among outpatients are attributed to PHPT, whereas in ill and hospitalized patients, malignancy constitutes more than half of all the cases.[1]

Hitherto, data on the prevalence and profile of hypercalcemia in hospitalized Asian–Indian patients are limited. A study conducted in a tertiary care hospital in North India found that 537 out of 26,297 patients had sustained hypercalcemia, amounting to an incidence of 2.09%. The most common cause of sustained hypercalcemia was malignancy (23.1%), followed by (PHPT, 21.9%). However, the study had certain limitations, including a retrospective design and lack of follow-up data.[2] Considering the lacunae in the existing literature, we conducted a prospective observational study to determine the prevalence and etiological profile of hypercalcemia in hospitalized Asian–Indian patients and its association with 6-month mortality.

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Materials and Methods

Study design

We conducted a prospective observational study under the aegis of the department of endocrinology wherein all the patients (aged >12 years) admitted to the general medicine wards (male medical ward and female medical ward) of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, between January 1, 2016, and June 30, 2017, were screened at admission irrespective of the working diagnosis. Finally, patients with sustained hypercalcemia were included in the study. The study was approved by the institute ethical committee, and written informed consent was taken from each study participant.

Sustained hypercalcemia was defined as corrected serum total calcium ≥10.4 mg/dl documented twice at least 24 h apart.[3] Serum calcium levels were adjusted for the corresponding serum albumin levels. Hypercalcemia was further categorized into mild, moderate, or severe as follows: mild hypercalcemia: corrected serum total calcium = 10.5–11.9 mg/dl; moderate hypercalcemia: corrected serum total calcium = 12.0–13.9 mg/dl; and severe hypercalcemia: corrected serum total calcium = 14 mg/dl or greater.

Patients with sustained hypercalcemia underwent further blood investigations, notably, serum creatinine, inorganic phosphate, magnesium, total alkaline phosphatase (ALP), plasma intact parathyroid hormone (iPTH), and 25-hydroxy Vitamin D. Hypercalcemia was categorized as PTH-dependent when plasma iPTH ≥20 pg/ml and PTH-independent when plasma iPTH <20 pg/ml.[4,5] Vitamin D intoxication was defined as plasma 25-hydroxyvitamin D >150 ng/ml along with a suppressed iPTH.[6] Subsequently, appropriate imaging was performed to delineate the underlying etiology of hypercalcemia and included ultrasonography of the neck and/or $^{99\,m}$Tc-Sestamibi scan (for PTH-dependent hypercalcemia) or contrast-enhanced computed tomography (CT) of the body and/or ^{18}fluorodeoxyglucose positron emission tomography-CT (for PTH-independent hypercalcemia). Further workup for the etiological diagnosis was guided by the imaging findings. These patients with sustained hypercalcemia were followed up throughout the hospital course and thereafter telephonically every month till 6 months from the date of discharge.

Serum total calcium, albumin, inorganic phosphate, total ALP, and creatinine were measured by a spectrophotometric assay using an auto-analyzer (Roche diagnostics, Cobas C702, Germany). Plasma iPTH and 25-hydroxyvitamin D were measured by electrochemiluminescence immunoassay using an auto-analyzer (Roche diagnostics, Elecsys 2010 system, Germany). The reference range, limits of detection, and the coefficients of variation of the aforementioned parameters are summarized in Supplementary Table 1. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 22.0 software (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to check the normality of data. The normally distributed data were expressed as mean ± standard deviation (SD), while nonparametric data were expressed in median (interquartile range). Continuous variables associated with mortality were compared using the Independent Samples *t*-test or Mann–Whitney *U*-test, based on the normality of the data. For categorical variables, comparisons were made using Pearson Chi-square test or Fisher's exact test, as appropriate. After univariate analysis, binomial logistic regression analysis was used to delineate those variables predicting mortality. Finally, a receiver operating characteristics (ROCs) curve analysis was used to demarcate the serum total calcium cut off that would predict mortality with optimum sensitivity and specificity. A two-tailed $P < 0.05$ was considered to be statistically significant.

Results

During the study, 9902 patients aged >12 years were admitted to the male medical ward and female medical ward of PGIMER, Chandigarh, India. Of these 9902 patients, 150 patients had sustained hypercalcemia, amounting to a prevalence of 1.5%. The mean age (± SD) of the study population (n = 150) was 48.8 ± 14.6 years (range of 13–75 years).

Out of these 150 patients, 43.3% had mild hypercalcemia, 48% had moderate, and 8.7% had severe hypercalcemia. Figure 1 depicts the various etiologies of hypercalcemia and their corresponding frequencies. The most common etiology of hypercalcemia was malignancy (solid organ malignancy in 32 (21.3%) and multiple myeloma in 30 (20%) patients), followed by PHPT, which was seen in 49 (32.7%) patients. Other etiologies in the decreasing order of frequency were Vitamin D intoxication (n = 12, 8.7%), sarcoidosis (n = 8, 5.3%), tertiary hyperparathyroidism (n = 5, 3.3%), tuberculosis (n = 4, 2.7%), chronic liver disease (CLD) (n = 4, 2.7%), drug-induced (n = 3, 2%), and one case each of acromegaly and leprosy. Nevertheless, despite detailed investigations, the etiology of hypercalcemia could not be ascertained in 11 (7.3%) patients. Of note, the total number exceeds 150 as ten patients had more than one etiology of hypercalcemia.

The most common malignancy causing hypercalcemia was multiple myeloma, contributing to 30 cases, followed by squamous cell carcinoma of the lung (8 cases). Others in decreasing order were acute leukemia, lymphoma, chronic lymphoproliferative disorder, unknown primary with metastasis, adenocarcinoma lung, carcinoma gall bladder, carcinoma breast with metastasis, hepatocellular carcinoma, carcinoma tongue, carcinoma cervix, and splenic hemangiopericytoma.

The most common cause of PTH-dependent hypercalcemia was PHPT. Except for one patient with multiple endocrine neoplasia type 1 syndrome and another patient with breast parathyromatosis, all patients with PHPT had a solitary parathyroid adenoma. The

most common site of the culprit parathyroid adenoma was left inferior parathyroid adenoma (46.9%), followed by right inferior parathyroid adenoma (RIPA) (38.8%), ectopic PHPT (4.1%), left superior parathyroid adenoma (4.1%), and right superior parathyroid adenoma (4.1%).

Eleven patients with hypercalcemia had CLD of various etiologies. Out of these 11 patients, 7 had other comorbidities, notably, pulmonary tuberculosis (n = 2), carcinoma of the cervix (n = 1), RIPA (n = 1), abdominal tuberculosis (n = 1), multiple myeloma (n = 1), and hepatocellular carcinoma (n = 1), which might have contributed to the underlying hypercalcemia. However, no definite etiology of hypercalcemia could be found in four patients, hence, they were attributed to CLD *per se*.

The in-hospital management of hypercalcemia included saline diuresis in all patients. Apart from these, most patients with malignancy-related hypercalcemia (94%) required one or more drugs for the correction of hypercalcemia, notably, subcutaneous calcitonin, and/or zoledronic acid/denosumab. All patients with PHPT and tertiary hyperparathyroidism underwent successful excision of the culprit parathyroid lesions. All patients with Vitamin D intoxication and sarcoidosis were treated with oral corticosteroids. Eight out of 150 patients (5%) required one or more hemodialysis sessions to correct severe hypercalcemia.

Out of the 150 patients with hypercalcemia, 42 (28%) had died at the end of 6 months of follow-up [Table 1]. Patients with malignancy had the highest mortality rate, followed by those with an unknown etiology of hypercalcemia, tuberculosis, multiple myeloma, drug-induced hypercalcemia, Vitamin D intoxication, and CLD. We found that the mortality at 6 months in patients with multiple myeloma was 33%, whereas, in other malignancies, the cumulative mortality was 72%. No mortality was observed in patients with PHPT, sarcoidosis, tertiary hyperparathyroidism, and leprosy.

Univariate analyses showed that patients who had died were more likely to have an underlying malignancy, more likely to be males (P = 0.03), had significantly higher serum total calcium (P = 0.048), and lower hemoglobin levels (P = 0.028). There were no significant associations between mortality and other variables, notably age, eGFR, albumin, inorganic phosphate, iPTH, or 25-hydroxyvitamin D. Binomial logistic regression analysis showed that the mortality was significantly associated with the presence of an underlying malignancy and serum total calcium. In patients with mild, moderate, and severe hypercalcemia, mortality was 18.5%, 33.3%, and 46.2%, respectively. ROC analysis showed that the serum total calcium at which the risk of mortality was significantly increased was 12.25 mg/dl with a sensitivity of 61.9% and a specificity of 56% [Figure 2].

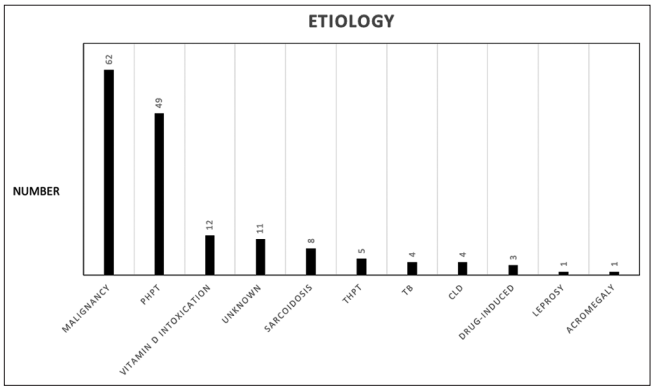

Figure 1: Diagram showing the various etiologies of hypercalcemia and their frequencies

Discussion

In this prospective observational study, we found that the prevalence of sustained hypercalcemia among patients

Table 1: Mortality in various etiologies of hypercalcemia

Etiology	Mortality
Solid organ malignancy	(23/32) 71.9%
Multiple myeloma	(20/30) 66.6%
Unknown	(5/11) 45.4%
Tuberculosis	(2/4) 50%
Drug-induced	(1/3) 33%
Vitamin D intoxication	(3/12) 25%
Chronic liver disease	(2/4) 50%
Sarcoidosis	(0/8) 0%
Tertiary hyperparathyroidism	(0/5) 0%
Leprosy	(0/1) 0%
Primary hyperparathyroidism	(0/49) 0%
Acromegaly	(0/1) 0%

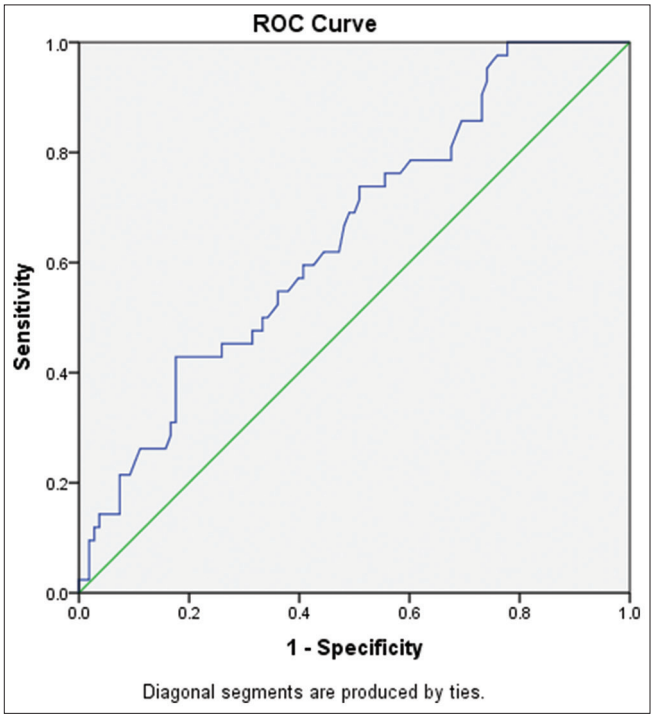

Figure 2: ROC curve showing that the corrected calcium levels positively correlated with mortality. ROC: Receiver operating characteristic

admitted to the general medicine wards of a tertiary care hospital was 1.5%. The most common cause of hypercalcemia was malignancy (41.3%), followed by PHPT (32.7%). Vitamin D intoxication was responsible for hypercalcemia in nearly one-tenth of patients. At the end of 6 months of follow-up, the cumulative mortality rate was 28%. Underlying malignancy and higher calcium levels were the significant determinants of mortality.

Hypercalcemia is a common electrolyte abnormality, which, if left undiagnosed, could lead to significant morbidity and mortality. Hence, early detection and correction of hypercalcemia are of paramount importance. Nevertheless, hypercalcemia is a surrogate marker of an underlying pathology that could range from a sinistrous entity like malignancy to a benign entity like familial hypocalciuric hypercalcemia. Thus, the presence of hypercalcemia should always warrant a thorough search for an underlying disease entity. In fact, in most cases, treatment of the underlying etiology often leads to the correction of hypercalcemia.

The etiology of hypercalcemia varies according to the clinical setting. The most common cause of hypercalcemia in outpatients is PHPT, the third most common endocrine disorder after diabetes mellitus and thyroid disorders. On the contrary, malignancy remains the most common cause of hypercalcemia in hospitalized patients. A prospective study conducted at a referral institution in South Africa had screened 58053 in-hospital patients over 12 months. The incidence of hypercalcemia was 0.6%, being transient in 19.2% of patients and sustained in the remainder. The most common causes in the sustained group were malignancy (45%) and PHPT (16.5%). Less common causes included renal disease (THPT), rhabdomyolysis, thyrotoxicosis, sarcoidosis, and lithium therapy. The lung was the most common primary site among the malignancies, followed by urogenital, gastrointestinal, hematological, and head and neck.[7] Another study conducted in the Emergency Department of the Inselspital Bern, Switzerland, from 2010 to 2011 showed that out of 8270 patients with available calcium measurements, 113 had hypercalcemia.[8] In yet another retrospective study conducted in the Emergency Department of a hospital in Taiwan, 321 of 4293 patients (7.5%) were found to have hypercalcemia. The most common cause of hypercalcemia was malignancy (117/321, 36.4%), followed by uremia (104/321, 32.4%). There were 99 patients on chronic maintenance hemodialysis and another five on peritoneal dialysis. Most patients had received calcium supplements containing 1,25-dihydroxy Vitamin D. The third largest number of cases (14.3%) was of unknown origin.[9]

Similar data from India are scarce. A retrospective study was undertaken to determine the profile of hypercalcemia in all patients who presented to a tertiary care hospital in North India. A total of 255830 patients presented to the hospital from January 1, 2014, to June 30, 2015 (18 months). Among them, calcium measurement was done in 26297 (10.2%) patients. A total of 552 patients were found to have hypercalcemia. Of these 552 patients, 15 (2.7%) patients had transient hypercalcemia and 537 (97.3%) had sustained hypercalcemia. The incidence of hypercalcemia was 2.09%, being transient at 0.05% and sustained at 2.04%. The most common cause in the sustained group was malignancy (23.1%), followed by PHPT (21.9%). Most cases of PHPT were asymptomatic. A significant number of patients had hypercalcemia of advanced CLD ($n = 34$) and Vitamin D intoxication ($n = 21$). Nevertheless, the study did have certain lacunae. The study had a retrospective design; besides, being a cross-sectional study, follow-up data, and clinical outcomes were not available.[2]

To overcome the aforementioned limitations, we had conducted the present study. The study had a prospective design and collated the follow-up data of the patients till 6 months from the date of discharge. Spanning over 18 months, we found that the prevalence of hypercalcemia in patients admitted to the general medicine wards was 1.5%. The most common etiology was malignancy, followed by PHPT.

Hypercalcemia of malignancy occurs in 5%–30% of patients with cancer during their illness, depending on the type of malignancy.[10] Breast and lung cancer account for >50% of all malignancy-associated hypercalcemia, whereas it is rare in colorectal and prostate cancer.[11] It is also important to note that hypercalcemia of malignancy is particularly common in cases of advanced stages of cancer. The mechanisms include direct skeletal metastasis, production of cytokines and PTHrP secretion by the malignant cells, increased ectopic activity of the enzyme 1-alpha hydroxylase, and subsequently increased formation of 1,25-dihydroxy Vitamin D (lymphomas and in some ovarian germ cell tumors).[12,13] However, more than one mechanism of hypercalcemia may be operational in a particular patient.[14] Except in patients with multiple myeloma and breast cancer, the prognosis of patients with hypercalcemia of malignancy is usually abysmal, with a mean survival rate of 2–3 months.[15]

The second-most common cause of hypercalcemia was PHPT. PHPT in India is predominantly a symptomatic disease, unlike in the West.[4,5,16] Nevertheless, with the widespread availability of auto-analyzers, early detection of PHPT at an asymptomatic stage is becoming more common in India. In the present study, all the patients with PHPT had a symptomatic disease. All patients underwent curative parathyroidectomy and none of the patients had died at the end of 6 months of follow-up.

Vitamin D intoxication is fast becoming one of the important causes of hypercalcemia.[4] Various studies conducted in India have demonstrated the rising trend of Vitamin D intoxication in the masses, primarily because of unsupervised usage of Vitamin D supplements, especially parenteral preparations.[17] The above-referenced study from North India did report a relatively high prevalence of Vitamin D

intoxication (n = 21, 5.5%).[2] Another study from North India reported an increasing trend for hypervitaminosis D from 1.48% to 7.82% over 6 years from 2011 to 2016.[18] Yet another case series from the Northern part of India had collated 16 cases of Vitamin D intoxication; the median (range) serum 25-hydroxyvitamin D level was 371 (175–1161) ng/ml.[6] We also observed a high prevalence of patients with Vitamin D intoxication (8.7%), all of whom had a history of multiple intramuscular injections in the recent past. Thus, irrational routine use of Vitamin D supplements, especially bolus parenteral preparations, should be discouraged. Besides, high-dose bolus replacement induces long-term expression of the catabolic enzyme 24-hydroxylase and fibroblast growth factor 23 (FGF23). Increased expression of 24-hydroxylase leads to diversion of 25-hydroxyvitamin D to inactive 24,25-dihydroxy Vitamin D while FGF23 leads to inactivation of the renal 1 α-hydroxylase that reduces the generation of the active metabolite, calcitriol.[19]

Hypercalcemia occurring in the setting of advanced CLD in the absence of any hepatic malignancy is a rare and poorly understood condition. This clinical condition should be kept in mind while evaluating the cause of hypercalcemia in CLD, irrespective of the etiology of the liver disease. It is a diagnosis of exclusion.[20] The prior study from India showed that 8.9% of the patients had hypercalcemia of advanced CLD.[2] In the present study, 11 patients had concurrent CLD, nevertheless, out of these 11 patients, 7 had another concurrent cause of hypercalcemia, hence, could not be solely attributed to CLD. Only four patients were labeled as having hypercalcemia of advanced CLD.

The cumulative mortality rate in the present study at the end of 6 months of follow-up was 23.1%; expectedly, patients with malignancy had the highest mortality rate. Because hypercalcemia usually occurs in advanced cancer cases or the terminal stage, it is regarded as a marker of poor prognosis. Such patients' average survival is typically several weeks.[21] Besides, serum calcium also emerged as a significant independent predictor of cumulative mortality, with the death rate being higher in those with moderate-severe than those with mild hypercalcemia. In line with our findings, Lee *et al*. reported that serum calcium was an independent risk factor for mortality in patients with hypercalcemia admitted to the emergency department.[9]

We do acknowledge the limitations of the study. First, in some patients, the underlying etiology of hypercalcemia could not be ascertained even after extensive workup. Second, to delineate the exact mechanism of hypercalcemia of malignancy or hypercalcemia related to granulomatous diseases, other biochemical parameters such as PTHrP and 1,25-dihydroxy Vitamin D could not be done due to nonavailability. Third, as the study was limited to the general medicine wards, the same cannot be generalized to the emergency setting.

Conclusions

The prevalence of hypercalcemia in Asian–Indian patients admitted to the general medicine wards of a tertiary care hospital was 1.5%. The most common etiology was malignancy, followed by PHPT. On follow-up, the cumulative mortality rate was 28%. The presence of an underlying malignancy and serum calcium level were independent predictors of the risk of mortality.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1; The reference range, dynamic measurement range, and coefficient of variation of the biochemical and hormonal parameters analyzed in the present study

Parameter	Reference range	Dynamic measurement range	Coefficient of variation (%)
Total calcium (mg/dl)	8.6-10.4	0.8-20.1	0.7
Inorganic phosphate (mg/dl)	2.4-4.5	0.31-20.0	0.9
Albumin (g/dl)	3.97-4.94	0.2-6.0	0.5
Total ALP (IU/l)	35-129	5-1200	0.7
Creatinine (mg/dl)	0.5-1.2	0.17-24.9	2.3
iPTH (pg/ml)	15-65	1.2-5000	1.5
25-hydroxy Vitamin D (ng/ml)	11.2-42.8	3-100	3.4

ALP: Alkaline phosphatase, iPTH: Intact parathyroid hormone