Original Article

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Aetiological Profile and Treatment Response of Patients with Hypercalcaemia: A Prospective Observational Study from a Tertiary Care Centre in Southern India

Internal Medicine Section

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ABSTRACT

Introduction: Hypercalcaemia requiring nephrologist care is relatively uncommon and represents a select subgroup of patients who are more severe and complex with metabolic derangements and renal failure. Aetiological profiling of hypercalcaemia is important in this regard for its appropriate management.

Aim: The present study aimed to identify the aetiological profile of hypercalcaemia and assess treatment response in patients presenting to a tertiary care centre in South India.

Materials and Methods: The current prospective observational study was conducted at St Johns Medical college hospital, Bangalore, Karnataka, India from January 2024 to September 2025, including 27 adult patients (>18 years) with persistent corrected calcium levels >10.5 mg/dL. Aetiology was determined using biochemical markers and imaging. Patients were followed for 30 days to assess treatment response and outcomes. Frequencies and standard deviations were calculated. Chi-square test was applied for categorical data analysis. Paired t-test was used to analyse treatment outcome.

Results: The mean age was 53.8±14.4 years, with 55.6% females. The mean serum calcium at presentation was 12.98±1.74 mg/dL. The most common aetiologies were malignancy (37.03%, n=10, primarily plasma cell dyscrasia at 25.92%), followed by primary hyperparathyroidism (parathyroid adenoma, 22.20%, n=6) and iatrogenic causes (22.20%, n=6). Other causes included sarcoidosis (11.10%, n=3) and infective (7.40%, n=2). Mean calcium decreased to 9.17±1.07 mg/dL after 30 days in 24 patients. Notably, 40.74% had pre-existing Chronic Kidney Disease (CKD), and 12 out of 16 patients developed Acute Kidney Injury (AKI) secondary to hypercalcaemia. Non-specific symptoms like nausea/vomiting (77.77%) and fatigue (66.66%) were prominent. The cumulative mortality rate was 11.11% (n=3).

Conclusion: Malignancy, primary hyperparathyroidism, and iatrogenic causes are the predominant aetiologies of hypercalcaemia in this region. Non-specific symptoms should prompt early suspicion. Increased awareness of judicious vitamin D supplementation as well as periodic health check is crucial to mitigate iatrogenic hypercalcaemia.

Keywords: Haemodialysis, Hyperparathyroidism, Plasma cell dyscrasia, Renal failure

INTRODUCTION

Hypercalcaemia arises from various underlying aetiologies and is defined as serum calcium level >10.5 mg/dL or 2.5 mmol/L [1]. Hypercalcaemia can be further classified as mild 10.5 to 11.9 mg/dL (2.5-3 mmol/l), moderate 12 to 13.9 mg/dL (3-3.5 mmol/l) and severe >14 mg/dL (3.5 mmol/l) [2]. Primary hyperparathyroidism and malignancy account for more than 90% of hypercalcaemia. Parathyroid adenoma accounts for the majority of cases of primary hyperparathyroidism [3]. Other causes include iatrogenic factors (vitamin D and calcium supplements), as well as lung diseases like sarcoidosis and tuberculosis [4]. Manifestation of hypercalcaemia is usually noted once the serum calcium level increases above 12 mg/dL, which is classically described as "bones, stones, groans and moans" [5]. Serum calcium, vitamin D, and Parathyroid Hormone (PTH) levels should also be estimated to delineate hypercalcaemia as PTH-dependent or PTH-independent. Profiling of hypercalcaemia is necessary for its accurate diagnosis, appropriate management and improved clinical outcomes.

Hypercalcaemia presenting to emergency department of a hospital has been well studied [6-8], however, there are no data on profile of Indian patients presenting with hypercalcaemia requiring nephrology intervention. These prior studies [6,8] had certain limitations being retrospective in nature and lacked follow-up data. The present study aims to identify the aetiological profile of patients with hypercalcaemia presenting/referred to nephrology care at a centre in South India and assess the response to therapy. The approach towards hypercalcaemia from a nephrological perspective adds a new dimension in the outcome of patient. Hence the current study was carried out.

MATERIALS AND METHODS

The present prospective observational study of all patients admitted at/referred to the Department of Nephrology at St Johns medical college hospital, Bangalore, Karnataka, India between 1st January 2024 to 30th September 2025 was conducted. Patients with sustained hypercalcaemia were included. The study was approved by the Institutional Ethical Committee. (Ref no. 341/2024).

Inclusion and Exclusion criteria: Patients aged above 18 years with a persistent corrected calcium value greater than 10.5mg/dL on two consecutive days were included in the study. Data from patients who were pregnant were excluded. It was a time bound study conducted in a fixed time line. All patients who fulfilled the inclusion criteria, and presented during the study period were included as samples and were followed-up for one month after treatment initiation.

Study Procedure

Sustained hypercalcaemia was defined as persistent hypercalcaemia documented on two consecutive days [9]. Hypercalcaemia was

divided into mild (calcium 10.5 to 11.9 mg/dL), moderate (calcium 12 to 13.9 mg/dL) and severe (calcium greater than 14mg/dL). Other parameters like serum creatinine (mg/dL), serum albumin (g/dL), serum phosphorus (mg/dL), Alkaline Phosphatase (ALP, in U/L), vitamin D (ng/mL), serum intact PTH (iPTH), and Angiotensin converting enzyme (U/L) levels were noted. Serum creatinine was estimated and patients were classified into having AKI [10] and CKD [11] as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria respectively. Serum albumin was estimated for corrected calcium calculation.

Wherever applicable, patients were subjected to the following imaging modalities: chest X-ray, ultrasonography of neck and abdomen, technetium 99 m sestamibi scan, computed tomography and 18F-fluorodeoxyglucose positron emission tomography-CT to identify the cause of hypercalcaemia. Hypervitaminosis D was considered when the plasma 25 hydroxy vitamin D level was >150 ng/mL along with suppressed iPTH [12]. Hypercalcaemia was further divided as PTH-dependent when plasma iPTH >20 pg/mL and PTH independent when plasma iPTH <20 pg/mL [13]. Patient's details were followed up for a period of 30 days after initiation of treatment. All patients who achieved normal calcium at the end of 30 days of study were considered as response to therapy.

STATISTICAL ANALYSIS

Data entered into Microsoft (MS)-excel and analysis done using statistical software IBM Statistical Package for the Social Sciences (SPSS) software version 26.0. Frequencies and percentages calculated for categorical variables. Descriptive statistics were calculated (mean and standard deviations) for continuous variables. Chi-square test was used to test the requirement of dialysis in CKD and AKI patients respectively. Paired t-test was used to compare serum calcium levels at admission and at the end of one month after treatment.

RESULTS

A total of 27 patients with persistent hypercalcaemia were included in the study. A 55.6% (n=15) were females and 44.4% (n=12) were males. The aetiological spectrum of hypercalcaemia at presentation, with frequency, is depicted in [Table/Fig-1] below. All except three patients who expired completed the evaluation period of one month of follow-up.

Causes	Frequency	Percentage (%)
Non-myeloma malignancy	3	11.10%
Plasma cell dyscrasia	7	25.92%
Iatrogenic	6	22.20%
Infective	2	7.40%
Sarcoidosis	3	11.10%
Parathyroid adenoma	6	22.20%
Total	27	100.00%

[Table/Fig-1]: Aetiological spectrum of hypercalcaemia and its frequency.

The mean age at presentation was 53.8±14.4 years. mean serum calcium at presentation was 12.98±1.74 mg/dL. 25.92 % patients had mild (n=7), 44.44% had moderate (n=12), and 29.62% (n=8) had severe hypercalcaemia. At the end of 30 days after treatment, the mean calcium level was 9.17±1.07 mg/dL in 24 surviving patients [Table/Fig-2]. The means of all the variables considered for the study are mentioned in [Table/Fig-2]. Fifteen patients had PTH-independent and 12 patients had PTH-dependent hypercalcaemia at presentation, as depicted in [Table/Fig-3,4], respectively.

The commonest cause of hypercalcaemia was malignancy (37.03%, 10 out of 27 patients). Plasma cell dyscrasias were the most common malignancy, contributing to 25.92% (n=7) at presentation.

Variables	n	Mean
Age (in years)	27	53.81±14.4 years
Corrected Calcium at admission	27	12.98±1.74 mg/dL
Serum Phosphorus	27	3.39±2.02 mg/dL
Alkaline Phosphatase (ALP)	27	212.85±166.14 U/L
Vitamin D	27	99.2±64.82 ng/mL
Parathormone (PTH)	27	309.34±601.03 pg/mL
Angiotensin converting enzyme (ACE)[$]	7	43.41±34.05 U/L
Corrected calcium at end of 30 days*	24	9.17±1.07 mg/dL
Average serum creatinine at the end of 30 days*	24	3.02±3.09 mg/dL

[Table/Fig-2]: Metabolic parameters of the study group.
[$]ACE levels were analysed for only those 7 patients with strong suspicion of sarcoidosis,
*Rest 3 patients died and couldn't complete the study

Total no. of patients	n=15
Plasma cell dyscrasia	7
Non myeloma malignancy	3
Sarcoidosis	3
Infective	2

[Table/Fig-3]: PTH- independent causes of hypercalcaemia.

Total no. of patients	12 (%)
Parathyroid adenoma	6 (22.20%)
Iatrogenic	6 (22.20%)

[Table/Fig-4]: PTH-dependent causes of hypercalcaemia.

Five out of seven patients who were diagnosed with plasma cell dyscrasia were females, among whom three were elderly, aged above 60 years. All seven patients had low serum ALP levels. This was attributed to the suppressed osteoblastic activity caused by myeloma cells and low bone turnover.

The non-myelomatous malignancies that presented were one case each of breast cancer with bone metastasis, nasopharyngeal carcinoma and one lymphoma with skeletal metastasis. All three patients had AKI, with one requiring a few sessions of haemodialysis as well during the course. Six patients (4 males and 2 females) who had primary hyperparathyroidism were diagnosed with parathyroid adenoma, contributing to 22.2%. All six underwent parathyroidectomy as part of treatment. One out of these six patients presented with features of pancreatitis.

Vitamin D intoxication is also one of the leading causes of hypercalcaemia. 22.2% patients (n=6) in the study group had iatrogenic hypercalcaemia, mainly due to increased calcium and vitamin D supplements. All six patients had CKD, and five of them required regular maintenance haemodialysis. All six had high PTH values attributable to long standing CKD and tertiary hyperparathyroidism [14]. Four out of these six patients had associated hyperphosphatemia which was attributed to increased phosphate absorption from the gut secondary to hypervitaminosis and reduced renal clearance.

An 11.11% (n= 3) of patients were diagnosed with sarcoidosis. All three of them had increased Angiotensin-Converting Enzyme (ACE) levels. Two patients had AKI, which resolved, and one had underlying CKD on conservative management. Steroids and hydroxychloroquine were used for treatment. Hypercalcaemia resolved in all these at the end of one month of therapy. Two patients in the study group were diagnosed with tuberculosis. Both patients had underlying CKD.

A 40.74% (11 out of 27) patients included in the study had pre-existing CKD, out of which seven required regular maintenance haemodialysis (25.92%), and one required temporary dialysis in view of hypercalcaemia. Amongst all CKD patients, five had PTH independent and six PTH dependent hypercalcaemia, respectively.

Among the 16 patients who did not have preexisting CKD, 12 had AKI attributable to hypercalcaemia. In the rest, two patients had associated sepsis, and two had underlying drugs as the associated contributing factor for AKI. Three patients with AKI required temporary sessions of dialysis. In 10 out of 16 patients (62.5%), AKI completely recovered by day 30 after treatment. [Table/Fig-5,6] depict AKI and CKD results, respectively. Also, [Table/Fig-7] gives the comparative data of the outcomes based on aetiology of presentation.

Outcomes	n
Patients with AKI (as per KDIGO) at presentation	16
Patients with resolution of AKI at the end of 1 month	10
Patients with AKI requiring temporary haemodialysis	3

[Table/Fig-5]: Outcomes of AKI.

Outcomes	n
Total patients with CKD	11
Regular maintenance haemodialysis	7
Temporary dialysis	1

[Table/Fig-6]: Outcomes of CKD with hypercalcaemia.

Disease	Total no	AKI	CKD	Required haemodialysis	Hypercalcaemia resolved	Died
Non Myelomatous malignancy	3	3	0	1	2	1
Plasma cell dyscrasia	7	7	0	2	7	0
Iatrogenic	6	0	6	5	4	2
Infective	2	0	2	1	2	0
Sarcoidosis	3	2	1	0	3	0
Parathyroid adenoma	6	4	2	2	6	0

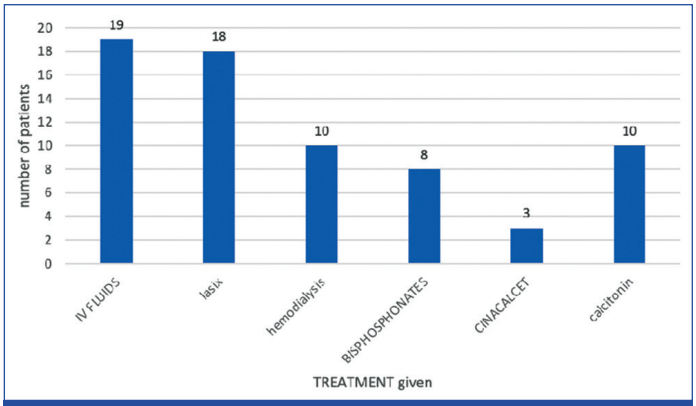
[Table/Fig-7]: Outcomes as per aetiology.

At presentation patients had various combinations of symptoms. Nausea and vomiting were observed as the major symptom at presentation in 77.77% individuals (n=22). Fatigue was the next common complaint seen in 66.6% individuals (n=18). 62.96% patients had associated abdominal pain (n=17). Neurological manifestation in the form of irritability, altered sensorium, and confusion was seen only in 11.11% individuals (n=3). One patient had associated seizures requiring dialysis. Three patients (11.11%) had associated pancreatitis, wherein symptoms subsided after treatment.

Most patients were managed with a combination of saline diuresis and intravenous furosemide. Also, patients with hypercalcaemia of malignancy received subcutaneous calcitonin and or denosumab when required. Patients with primary and tertiary hyperparathyroidism received cinacalcet. All patients with parathyroid adenoma underwent parathyroid excision. Patients with sarcoidosis and vitamin D intoxication received oral steroids. Treatment given is depicted in the [Table/Fig-8].

Contributing factors for renal replacement therapy (haemodialysis) in hypercalcaemia patients were looked at and amongst age, gender, malignancies, diabetes, hypertension and pre-existing CKD; it was observed that more patients with pre-existing CKD required haemodialysis as part of treatment for hypercalcaemia with significant p-value (0.0176<0.05) [Table/Fig-9]. The serum calcium levels after successful treatment at the end of observation period of one month was significantly lower (12.98±1.74 mg/dL Vs 9.17±1.07 mg/dL; p<0.001).

Hypercalcaemia resolved in 24 patients at the end of one month of initiation of treatment; three patients succumbed. Among the patients who died, two had underlying CKD, and one was diagnosed with



[Table/Fig-8]: Treatment received by the patients.

Variables	p-value	Result
Age (≤60 years and >60 years) vs requirement of dialysis	0.8086	Not significant
Gender (male and female) vs requirement of dialysis	0.6559	Not significant
Aetiology (malignancy and non malignancy) vs requirement of dialysis	0.5614	Not significant
Diabetes vs requirement of dialysis	0.0741	Not significant
Hypertension vs requirement of dialysis	0.5812	Not significant
Pre-existing chronic kidney disease (ckd) vs requirement of dialysis	0.0176	Significant

[Table/Fig-9]: Factors associated with requirement of dialysis.

B-cell leukaemia with multiple lung and skeletal metastases. Among the patients with CKD who died, one had ventricular tachycardia and cardiac arrest; sepsis with shock was attributed in other as the contributing factor for death.

DISCUSSION

The aetiological profile of hypercalcaemia remains varied. However, malignancy and primary hyperparathyroidism are the two common causes of hypercalcaemia [15,16]. At the end of study, it was found that malignancy (37.03%) was the most common cause of hypercalcaemia, followed by primary hyperparathyroidism and vitamin D intoxication (22.2%). At the end of 30 days, the cumulative mortality was 11.11%. Plasma cell dyscrasias contributed to the majority (25.92%) of the malignant cases. A similar study done from North India showed 537 patients had sustained hypercalcaemia, with most common cause being malignancy (23.1%) followed by primary hyperparathyroidism (21.9%) [6]. However, a South African study showed lung cancer as the most common primary tumour to cause malignancy. Primary hyperparathyroidism (16.5%) was the second most common cause of hypercalcaemia after malignancy (45%) [7]. Yet another retrospective study done at emergency department of a hospital at Taiwan showed 321 out of 4293 patients (7.5%) to be having hypercalcaemia with malignancy being the most common cause [8].

Hypercalcaemia secondary to malignancy has been observed in 5-30% cases with cancer, depending on the type of malignancy [17]. This is attributed to excessive secretion of Parathyroid Hormone-Related Protein (PTHrP), bony metastasis releasing osteoclast activating factors, and production of 1,25-dihydroxy vitD (calcitriol) [18]. Multiple Myeloma and other solid organ tumours with bone metastasis release osteoclast-activating factors, causing hypercalcaemia. They present with low to normal PTH, and 1,25-dihydroxyvitD [19]. All seven patients diagnosed with plasma cell dyscrasia in the study group had low-normal iPTH levels. Five out of those seven patients also had associated low vitamin D. Non-myelomatous malignancies contributed to 11.11 % (n=3) of total cases. Two out of those three patients had skeletal metastasis. They also had low PTH. Two of those patients had a low level of vitamin D as well. These findings correlated well with the study by Guise TA et al., [19].

Vitamin D intoxication is one of the important curable causes for hypercalcaemia [15]. This is mainly due to an increase in the usage of vitamin D supplements [20]. An increase in the trend of hypervitaminosis D from 1.48 to 7.82% over six years was reported in a North Indian study [21]. In the current study, six out of 27 patients (22%) had iatrogenic hypercalcaemia attributable to excessive vitamin D, calcium and calcium-based phosphate binders' supplementation. All these contribute to positive calcium balance leading to vascular, and soft-tissue calcification, thereby increasing the risk of cardiovascular mortality and morbidity. Health professionals and the general public's awareness about vitamin D toxicity and the judicious use of its supplements are the main factors to prevent this. Periodic medical consultation and monitoring of serum calcium and 25- hydroxyvitamin D levels should be emphasised upon.

Granulomatous disease association with Hypercalcaemia was established in 1939 [22]. In India, sarcoidosis [23], tuberculosis [24], and leprosy [25] are some of the common granulomatous diseases associated with hypercalcaemia. In the present study, two patients with tuberculosis (7.40%) and three with sarcoidosis (11.11%) presented with hypercalcaemia. Out of the two tuberculosis cases, one had disseminated disease. At the end of 30 days, in both patients with tuberculosis and sarcoidosis, serum calcium levels normalised. Hypercalcaemia in granulomatous diseases is attributed to excessive production of 1,25 hydroxy vitamin D by macrophages within the granulomas. This increases calcium absorption in the gut, causing hypercalcaemia and suppressed PTH values [26]. Even in this study, both patients with tuberculosis had low PTH values. Two out of the three patients diagnosed with sarcoidosis had low PTH, and one had a low normal value.

A Chinese study found that hypophosphatemia is the 2nd most common electrolyte abnormality in cancer patients [27]. Fibroblast Growth Factor (FGF) secreted by osteocytes acts on the distal nephron to increase phosphate excretion by internalisation of sodium. It downregulates activation of 1,25-dihydroxy cholecalciferol, reducing the phosphate absorption from the gut [28]. Also, in Multiple myeloma, the tubular damage induced by light chains causes Fanconi's syndrome, resulting in hypophosphatemia [29,30]. Even in the present analysis, it was found that all seven patients who were diagnosed with multiple myeloma had associated hypophosphatemia, correlating well with the above findings.

To the best of the authors' knowledge, none of the previous studies had looked into the various presenting features of hypercalcaemia among patients. In literature, presenting symptoms of hypercalcaemia are typically described as stones, groans and moans referring to the abdominal pain, renal calculi and neurological symptoms that are known to occur commonly with hypercalcaemia. However, in our study, we found that the most common presenting symptoms are very nonspecific, with nausea, vomiting (77.77%) and fatigue (66.6%) being the top three manifestations. 62.96% patients at presentation had associated abdominal pain. Neurological manifestations and pancreatitis were seen only in 11.11% of patients. Hence, it could be interpreted from the present study that adding to the classical presentation of hypercalcaemia, nonspecific symptoms like nausea, vomiting, and fatigue at initial presentation should also raise the suspicion towards early diagnosis of hypercalcaemia. The cumulative mortality rate in our study at the end of one month was 11.11%. Two out of those three deaths took place in patients with CKD. One had B cell lymphoma with skeletal and lung metastasis. Ventricular arrhythmia precipitated by hypercalcaemia in an underlying poorly functioning heart and sepsis with septic shock with multiorgan dysfunction was the attributed cause of death in CKD patients. Also, all the patients with malignancy presented very late to our centre. Lee CT et al., reported that serum calcium will be an independent risk factor for mortality in patients with hypercalcaemia presenting to the emergency department [8].

Limitation(s)

First, it was a descriptive study. Second, to delineate the exact mechanism of hypercalcaemia of malignancy or hypercalcaemia related to granulomatous diseases, other biochemical parameters, such as PTHrP, could not be done due to nonavailability. Thirdly, the sample size was small, and hence the result cannot be extrapolated to the general population.

CONCLUSION(S)

The profiling of hypercalcaemia is an intricate task that holds utmost importance. Though the spectrum of aetiologies of hypercalcaemia spans from primary hyperparathyroidism to malignancies, as healthcare professionals, we must recognise the dynamic presentations of hypercalcaemia through a systematic approach. With the varied clinical presentation, the imaging and laboratory tests add on as a tool to differentiate the aetiological spectrum of hypercalcaemia. Malignancy and primary hyperparathyroidism were the most common causes of hypercalcaemia in our hospital setting. Vitamin D intoxication/overdose is also an emerging cause of hypercalcaemia. About this, health care professionals and the public should be made aware of the injudicious use of vitamin D supplements as well.

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