Research Article

Journal of Anesthesia & Pain Medicine

Hypercalcemia in Cancer: Association with Malignancy Type and Effect on Mortality

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Submitted: 03 Aug 2016; **Accepted**: 09 Aug 2016; **Published**: 12 Aug 2016

Abstract

Purpose

Hypercalcemia is an electrolyte disorder found in cancer patients which can complicate the disease and hasten death. It is classified by a blood serum calcium level of 2.6 mmol/l and above and its incidence is related to malignancy type. The object of this study is to explore the distribution of hypercalcemia amongst different cancer forms and to record the effects on mortality. The study investigates the same factors with regards to moderate and severe hypercalcemia.

Methods

Medical records for 2048 patients admitted over a five year period (2008-12) to the National Centre for Cancer Care, Qatar, were retrospectively reviewed to establish calcium levels.

Results

Chi-square distinguished multiple myeloma, renal cell carcinoma and lung cancer as the most common malignancies associated with hypercalcemia in our sample. The malignancies that most commonly resulted in severe hypercalcemia were multiple myeloma, head and neck and renal cell carcinoma. Univariate analysis identified hypercalcemia, age, and gender and cancer type as predictive factors for survival over the period of the study. These factors were used to build a multivariate model which revealed cancer patients with hypercalcemia were three times more likely to die than patients with normal blood calcium levels. Expiry was also more probable in those above 65 years of age and unexpectedly, females. Another unanticipated finding was that the effects of moderate and severe hypercalcemia on mortality were similar.

Conclusions

The present study demonstrated that in a hospitalized cancer population, age, gender, cancer type, and hypercalcemia are prognostic factors for increased mortality. The marginal differences in mortality between those with moderate or severe hypercalcemia suggest that early detection and treatment of such electrolyte imbalance is warranted regardless of calcium severity.

Keywords: Hypercalcemia, Cancer type, Mortality.

Introduction

Hypercalcemia is a well-known electrolyte disorder classified as a calcium (Ca^{2+}) blood serum level of ≥ 2.6 mmol/l. It regularly occurs in hospitalized patients from malignant and non-malignant causes. The prevalence of high calcium is between 5-30% of cancer patients and prognosis is poor [1]. 80% of hypercalcemia patients die within one year, with many dying within 2-3 months [2]. The degree or severity of hypercalcemia is an important factor in the manifestation of symptoms [3-5]. Mild forms cause dehydration, nausea and fatigue whereas more severe cases lead to disorientation, coma or even death [5]. The decision to treat hypercalcemia is therefore complicated and there remains debate

amongst physicians as to the best course of action [6]. Malignancy type is a factor in predicting high Ca^{2+} levels. Elevated calcium levels are commonly associated with multiple myeloma (MM), breast and lung cancers, whilst renal, ovarian, head and neck (H&N) and prostate cancers are also prominently linked [7,5].

Cancers where the primary site of metastasis is bone record the highest incidences of hypercalcemia. 80% of MM patients for example, suffer from bone destruction with between 20-40% suffering from high calcium [8,3]. Similarly bone metastasis is common in breast cancer and 10-25% of patients will experience hypercalcemia during their illness [1].

Hypercalcemia in cancer patients is the most life threatening metabolic emergency in oncology [9,3]. Nevertheless, high Ca^{2+} can act as a marker for some forms of cancer and can be used to predict disease course [1]. Early detection and treatment of hypercalcemia therefore, is valuable in disease management and can reduce disease burden, improving quality of life [10]. This study aims to contribute to understanding hypercalcemia in hospitalized oncology populations by exploring the distribution of high Ca^{2+} amongst admitted patients with different diagnoses. A further purpose of this work is to identify which malignancies associate with high calcium and more specifically, which lead to moderate or severe hypercalcemia. To our knowledge few studies have compared the severity of blood Ca^{2+} between different cancer types. The study also tests the effects of hypercalcemia on mortality whilst controlling for calcium levels, age, gender and malignancy type.

Methods

Study sample

All male and female cancer patients, admitted to the National Center for Cancer Care and Research (NCCCR), Qatar, between January 1, 2008 to December 31, 2012 were enrolled in the study.

Data collection

After approval from the institutional review board at Hamad Medical Corporation, the medical records of all admitted patients were retrospectively accessed and demographic, calcium, malignancy and survival/mortality information recorded. Patient survival was monitored for a further two years from when the last participant was admitted onto the study (no other patients were recruited during this period). Hypercalcemia levels were taken within two months of diagnosis and the highest serum calcium reading was used in the analysis. Patients with serum albumin below 50 mg/dl had hypercalcemia levels corrected before being categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4 [11]. CTCAE classifies hypercalcemia into grades 1-4 with grade 4 the highest (≥3.4 mmol/l) and grade 1 the mildest (2.6-2.9 mmol/l). Using previous studies as guide participants were further ordered into moderate or severe hypercalcemia groups with CTCAE classifications 3 and 4 creating the severe group and CTCAE classifications 1 and 2, the moderate group [4].

Statistical analysis

Descriptive statistics (using SPSS v22) explored patient demographics before cross-tabulation was performed to compare over/under 65 year olds, as well as males/females, to the moderate and severe hypercalcemia groups within those with hypercalcemia. The same procedure was carried out to ascertain the highest frequencies of hypercalcemia, moderate or severe hypercalcemia for each malignancy type. The malignancies with the highest frequencies were compared to the remaining population (for hypercalcemia) and the hypercalcemia population (for moderate and severe) using Chi-square to determine significance.

Univariate analysis then tested the influence of hypercalcemia severity, age, gender and diagnosis on mortality. Variables that were significantly associated with mortality were included in a multivariate regression model to explore mortality whilst controlling for each factor.

Results

Demographics

Males (57.5%) were more prevalent than females (42.5%) (mean age 51.57 years SD ±15.17, range 14-99 years) (Table 1).Those over 65 years made up 19.8 % of the group with 80.2% being under. Qataris were the most highly represented nationality (24.5%), followed by Egyptians (10.6%), Indians (7.1%), Filipinos (6.8%) and Sudanese (6.3%). Sixteen other nationalities made up the remaining 44.6% of the cohort.

		Count (n)	Percentage (%)
Gender	Female	869	42.4%
	Male	1179	57.5%
Age	≥ 65	405	19.8%
	< 65	1643	80.2%
Nationality	Egyptian	218	10.6%
	Filipino	139	6.8%
	Indian	146	7.1%
	Other*	914	44.6%
	Qatari	501	24.5%
	Sudanese	130	6.3%

Table 1: Gender, age and nationality.

Hypercalcemia; frequency, severity and association with malignancy type

Descriptive statistics revealed that 18.7% of participants had blood serum calcium over 2.6 mmol/l. That represents 384 patients with men and those below 65 years of age more highly represented than women and people above 65 (Table 2). 81.8% of those with hypercalcemia were in the moderate group (15.3% of the whole cohort, n = 314) and 18.2% were in the severe category (3.5% of the whole cohort, n = 70). Males and patients below 65 years had higher percentages in the moderate category and patients below 65 and women appeared more frequently in the severe category. Within those with hypercalcemia, Chi-square revealed no significant distributions of gender or age in either moderate or

severe groups at the p = 0.05 level.

		Number with hypercalcemia (%) †	Number with moderate hypercalcemia (%) *	Number with severe hypercalcemia (%) *	p-value
Gender	Female	187 (9.1)	149 (38.8)	38 (9.9)	0.301
	Male	197 (9.6)	165 (43.0)	32 (8.3)	
Total		2048 (18.7)	314 (81.8)	70 (18.2)	
Age	≥ 65 years	104 (5.1)	87 (22.7)	17 (4.4)	0.561
	< 65 years	280 (13.6)	227 (59.1)	53 (13.8)	
Total		2048 (18.7)	314 (81.8)	70 (18.2)	

Table 2: The distribution of hypercalcemia (≥2.6 mmol/l), moderate hypercalcemia (2.6-2.9 mmol/l) and severe hypercalcemia (≥3.1 mmol/l) in relation to gender and age; † Percentage of those within the whole cohort, * Percentage of those within the hypercalcemia group.

Figure 1 shows the frequency distribution of patients with hypercalcemia within each malignancy subgroup. The groups with the highest frequency of hypercalcemia were MM (49.1%), renal cell carcinoma (RCC) (35.3%), cervical (25.8%), and lung (25.4%) cancers. Rectal and nasopharyngeal (NP) cancers were the least common types (8.2% and 8.6% respectively).* These malignancy groups were tested individually versus all other patients using Chi-square to determine whether observed differences were statistically significant. Results showed that MM ($\chi^2(1, n = 55) = 34.152$, $p < 0.0001$), RCC ($\chi^2(1, n = 34) = 6.212$, $p < 0.013$) and lung cancer ($\chi^2(1, n = 169) = 5.418$, $p < 0.02$), had significantly more patients with hypercalcemia than non-MM, non-RCC and non-lung cancer patients in our sample.

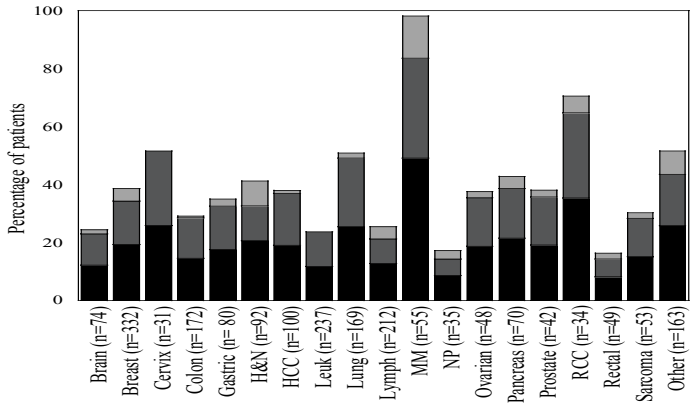

Figure 1: The distribution of hypercalcemia severity for each malignancy type. Black is the percentage of those with hypercalcemia in each malignancy. The percentages of moderate and severe amongst those with hypercalcemia are represented by grey and light grey respectively.

H&N = Head and Neck; HCC = Hepatocellular Carcinoma; Leuk = Leukemia; Lymph = Lymphoma; MM = Multiple Myeloma; NP = Nasopharyngeal; RCC = Renal Cell Carcinoma; Other = Anal; Appendicular; Cancer of unknown origin; Chondroma; Gastrointestinal stromal tumour; Mesothelioma; Melanoma; Neuroendocrine, Peritoneal, Primitive neuroectodermal tumour; Testicular; Vaginal; Vulvar; Uterine; Cholangiocarcinoma; Esophageal; Ureter and bladder cancers.

The same procedures were carried out for moderate and severe hypercalcemia with each malignancy group independently tested against all those with hypercalcemia. The malignancy types most commonly associated with moderate hypercalcemia were MM (34.5%), RCC (29.4%), cervical (25.8%) and lung (23.7%) with rectal (6.1%) and NP (5.7%) the least common. For severe calcium, MM (14.5%), H&N (8.7%) and RCC (5.9%) had the highest percentages with cervical cancer and leukemia the least common (zero patients in this group) (Graph 1). Chi-square found no malignancy type had significantly more patients with moderate or severe calcium than any other.

Mortality model

Table 3 shows the results of the univariate analysis that tested the effects of four covariates on mortality (hypercalcemia severity, age, gender and diagnosis). Being in any hypercalcemia group significantly affected survival at the p< 0.0001 level (hypercalcemia, CI = 2.637-4.4167; moderate, CI = 2.459-4.023; severe, CI = 1.642-4.436). Age (CI = 1.128– 1.757, p< 0.002), gender (CI = 1.129–1.624, p< 0.001) and diagnosis (p< 0.001) also significantly predicted mortality. For diagnosis, MM was used as the reference category and only people with brain (CI = 1.136-4.903, p< 0.021), lung (CI = 0.233-0.898, p< 0.002) gastric (CI =1.395-5.920, p< 0.002) and pancreatic cancers (CI = 1.686-7.517, p< 0.002) were more likely to have expired over the period of observation than those with MM. Leukemia and lymphoma patients were significantly more likely to be alive (CI = 1.693-6.199, p< 0.03 and CI = 1.136-4.903, p< 0.023 respectively).

The four predictive factors were included in a multivariate model which was significant ($\chi2 = 369.4$, df = 21, p< 0.0001). Following correction, people in the hypercalcemia, moderate or severe hypercalcemia groups were, 3, 2.9 and 2.4 times more likely to have expired than those without hypercalcemia. The model also revealed that males and patients under 65 were significantly less likely to have died than females and those above 65 (CI = 1.269-2.086, p< 0.0001, CI = 2.207-3.710, p< 0.0001). Patients with brain (CI = 2.109-10.00, p< 0.001), lung (CI = 2.364-9.503, p< 0.0001), gastric (CI = 1.931-8.996, p< 0.0001) and pancreatic cancer (CI =2.452-12.11, p< 0.0001) remained more likely to have expired than those with MM, however, following the correction, HCC sufferers were also less likely to survive than MM patients over the period of this research (CI = 1.238-5.516, p< 0.012).

1: Sample size = 2048 patients; **2:** Each category in diagnosis was compared to "MM" (multiple myeloma) patients to calculate odds ratios, 95% confidence intervals and p values; **3:** Ref = reference group; **4:** § Odds ratio of being alive; **5:** Model summary for multivariate analysis: -2 Log likelihood = 2312.38, Cox & Snell = 0.165, Nagelkerke = 0.226. Hosmer and Lemeshow Chi-square value =6.201, p = 0.63; *Hypercalcemia ≥ 2.6 mmol/l was used in the multivariate analysis.

	Variables	N[1] (%)	Deaths (% of N[1])	Odds Ratio[§]	95% Confidence interval	p value	Odds Ratio[§]	95% Confidence interval	p value
Hypercalcemia	<2.6 mmol/l	1664 (81.3)	513 (30.8)	*Ref*[$]	-	-	*Ref*	-	-
	≥2.6 mmol/l	384 (18.7)	229 (59.6)	3.315	2.637-4.4167	0.000	3.083	2.399-3.962	0.000
	Total	2048 (100)	742 (36.2)						
Moderate Hypercalcemia	2.6-2.9 mmol/l	1731 (85.5)	553 (31.9)	*Ref*	-	-	*Ref*	-	-
	Non-moderate	317 (15.5)	189 (59.6)	3.229	2.521-4.136	0.000	2.909	2.223-3.806	0.000
	Total	2048 (100)	742 (36.2)						
Severe Hyper-calcemia	<3.0 mmol/l	1981 (96.7)	702 (35.4)	*Ref*	-	-	*Ref*	-	-
	≥3.0 mmol/l	67 (3.3)	40 (59.7)	2.424	1.496-3.925	0.000	2.424	1.435-3.923	0.000
	Total	2048 (100)	742 (36.2)						
Age	<65 years	1643 (80.2)	464 (28.2)	*Ref*	-	-	*Ref*[$]	-	-
	≥65 years	405 (19.8)	218 (53.8)	3.392	2.687 – 4.282	0.000	2.861	2.207-3.710	0.000
	Total	2048 (100)	742 (36.2)						
Gender	Female	869 (42.4)	350 (40.3)	*Ref*	-	-	*Ref*[$]	-	-
	Male	1179 (57.6)	392 (33.2)	1.354	1.129– 1.624	0.001	1.627	1.269-2.086	0.000
	Total	2048 (100)	742 (36.2)						
Diagnosis[2]	MM	55 (2.7)	17 (30.9)	*Ref*	-	-	**Ref*[$]	-	
	Brain	74 (3.6)	38 (51.4)	2.359	1.136-4.903	0.021	4.593	2.109-10.00	0.001
	Breast	332 (16.2)	115 (34.6)	1.185	0.640-2.191	0.589	1.457	0.739-2.873	0.277
	Cervix	31 (1.5)	12 (38.7)	1.412	0.562-3.548	0.463	1.462	0.539-3.963	0.455
	Colon	172 (8.4)	53 (30.8)	0.996	0.516-1.921	0.989	1.410	0.697-2.853	0.340
	Gastric	80 (3.9)	45 (56.3)	2.874	1.395-5.920	0.004	4.168	1.931-8.996	0.000
	H&N	92 (4.5)	22 (23.9)	0.703	0.333-1.481	0.354	0.979	0.442-2.171	0.959
	HCC	100 (4.9)	44 (44.0)	1.756	0.877-3.519	0.112	2.613	1.238-5.516	0.012
	Leukemia	237 (11.6)	42 (17.7)	0.481	0.248-0.933	0.030	0.839	0.415-1.698	0.626
	Lung	169 (8.3)	100 (59.2)	3.240	1.693-6.199	0.000	4.739	2.364-9.503	0.000
	Lymphoma	212 (10.4)	36 (17.0)	0.457	0.233-0.898	0.023	0.706	0.344-1.449	0.342
	NP	35 (1.7)	5 (14.3)	0.373	0.123-1.126	0.080	0.771	0.245-2.429	0.658
	Ovarian	48 (2.3)	19 (39.6)	1.465	0.649-3.303	0.358	1.758	0.732-4.223	0.207
	Pancreas	70 (3.4)	43 (61.4)	3.560	1.686-7.517	0.001	5.449	2.452-12.11	0.000
	Prostate	42 (2.1)	20 (47.6)	2.032	0.884-4.674	0.095	2.324	0.946-5.710	0.066
	RCC	34 (1.7)	13 (38.2)	1.384	0.564-3.395	0.478	1.543	0.592-4.025	0.375
	Rectal	49 (2.4)	17 (34.7)	1.188	0.523-2.697	0.681	2.093	0.870-5.038	0.099
	Sarcoma	53 (2.6)	18 (34.0)	1.150	0.513-2.575	0.735	2.080	0.889-4.862	0.091
	Other	163 (8.0)	83 (50.9)	2.319	1.212-4.438	0.011	3.076	1.535-6.614	0.002
	Total	2048 (100)	742 (36.2)						

Table 3: Results of univariate followed by multivariate regression analysis.

Discussion

Hypercalcemia is commonly found in hospitalized patients and is prevalent in oncology. The primary aim of this study was to document the frequency of hypercalcemia, moderate and severe hypercalcemia, with associated malignancy types. A further objective was to test the effects of hypercalcemia on mortality.

The incidence of hypercalcemia in our cohort was 18.7% (n=384) which places our findings in the mid-range of previous studies that estimate hypercalcemia at 5-30% in cancer patients [1]. The finding that malignancies MM, lung cancer and RCC had significantly more patients with hypercalcemia was expected as these diagnoses are commonly associated with high Ca^{2+} [8,12,13].

MM is the most widespread malignancy where skeleton is the primary site and thus progressive osteolysis, aggressive bone destruction and elevated blood calcium occur [14,8]. At 2.7%,

our incidence of MM is higher than other studies which could be related to ethnic factors. People of African origin are twice as likely to have MM as European whites and a significant portion of our sample is drawn from African nations [15,16]. However, the influence of ethnicity on hypercalcemia has not been well explored.

The percentage of RCC patients with elevated calcium is slightly higher than other reports perhaps due to small absolute numbers [17]. However, it is not an uncommon association with 30-40% of RCC patients experiencing bone metastases [18,19]. Age and gender influence the development of hypercalcemia in RCC [20,21]. One third of our RCC patients were above 65 years and 85% were male suggesting these factors had some bearing on our results.

Our findings support previous studies showing hypercalcemia is highly associated with lung cancer [22]. This high prevalence is likely linked to lung cancer's established relationship to social/cultural factors such as smoking [23]. There was a high male/female ratio in our sample and smoking remains more common in men than women particularly in developing nations [24]. Squamous cell carcinoma (SCC) is one of the most common forms of lung cancer and is connected to smoking [25]. SCC is also more frequent in older populations and few malignancy types in our sample had more participants above 65 years of age than lung [26].

The incidence of moderate and severe hypercalcemia in the overall cohort was 15.3% and 3.5% respectively. Few studies describe specific cases of moderate hypercalcemia but Vassilopoulou-Sellin et al. report an incidence of severe hypercalcemia much lower than ours (0.52%) [4]. However, these authors used a much smaller sample (n = 40).

Unsurprisingly, the malignancies associated with moderate hypercalcemia mirrored the calcium distribution for the whole sample (e.g. MM, RCC, cervical and lung cancer). However, in the severe classification, H&N had the second highest association (with MM first and RCC third). Hypercalcemia of H&N is well-known and, as with lung cancer, exists more often in men with smoking a major risk factor [27]. H&N typically occurs during the late stages of disease and is an ominous prognostic sign which may explain the association with severe calcium found here [28].

The mortality model replicated established trends in oncology/hypercalcemia research. Age, having hypercalcemia and specific malignancy diagnoses all predicted survival. However, an uncommon finding was that women were more likely to have expired than men. There are a number of reasons why this may have occurred. Qatar's demographic (and our sample) is skewed towards males and those below 65 who are possibly more able to withstand disease and treatments. Women were overrepresented in the over 65 group (the ratio was 1:1) and members of this category were more likely to die. The largest malignancy group in this data set was breast cancer (n=332) which was almost exclusively female and where one third of patients died. More women than men featured in the severe hypercalcemia group and as has been mentioned, high calcium can be an indicator of serious complications. Regarding diagnosis, four malignancy types contributed more to mortality than MM. These were lung, brain, pancreatic and gastric cancers. These cancers are aggressive and their influence on mortality was unsurprising. However, while lung cancer is commonly associated with hypercalcemia, brain, pancreatic and gastric cancers are less so. Nevertheless high calcium has been described in gastrointestinal pancreatic and brain cancer patients [29-32]. Only hepatocellular carcinoma (HCC) was more significant than MM after correction. The prevalence of hypercalcemia in HCC has been reported at 5.2% and a consistent gender bias exists with male/female ratios of 2:1 to 4:1 [33,34]. Our data is at the high end of those studies with a male/female ratio of 4:1. Risk factors for HCC are cirrhosis of the liver and hepatitis C [35]. An interesting aspect to our sample was that 40% of HCC patients, originated from Egypt. It is suggested that the recognized hepatitis C epidemic affecting that country may have influenced our group although further investigation is needed [36].

An unanticipated finding was that marginal differences were observed in expiry between those with hypercalcemia, moderate or severe hypercalcemia. A significant number of moderate hypercalcemia patients (22.7%) appeared in the over 65 category which may be contributing to this result but it is also possible Qatar's demography (i.e. a younger, stronger population) is having an influence. It must also be considered that our sample consisted of admitted patients who tend to be sicker, suggesting many of our moderate hypercalcemia patients were already at greater risk of expiry.

Study limitations

Some aspects of this study suggest caution should be taken when interpreting the results. Due to the large volume of expatriates, many patients leave Qatar following diagnosis. It is assumed a significant percentage of these patients die at home meaning that mortality is underestimated in our sample. All participants were monitored for a minimum of two years meaning patients included early in the study had longer to expire. Our mortality model was biased therefore, by the inclusion of patients more recently diagnosed. Comorbidities, course or stage of treatment were not documented in this study. In addition, the effects of the demographic bias on survival between expatriates and the local population were not explored. The relationships between these factors and hypercalcemia are of notable interest and warrant inclusion in further studies.

Conclusion

The present study demonstrates four independent factors are associated with increased mortality among hospitalized cancer patients; hypercalcemia, diagnosis, age and gender. Minimal differences were detected in mortality between patients with moderate versus severe hypercalcemia suggesting that early detection and treatment of such electrolyte imbalance is justified regardless of calcium severity.

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