Medical Oncology (2019) 36:90
https://doi.org/10.1007/s12032-019-1315-8

SHORT COMMUNICATION

Outcomes of hypercalcemia of malignancy in patients with solid cancer: a national inpatient analysis

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Received: 27 July 2019 / Accepted: 8 September 2019

Abstract

Hypercalcemia of malignancy (HCM) is present in one-third of cancer patients and is associated with a significant mortality risk of 50% within 1 month of diagnosis. We aimed to study the impact and outcomes of HCM in hospitalized patients with solid cancer. We analyzed data captured in the National Inpatient Sample database of the Agency of Healthcare Research and Quality. The study included all hospitalizations in adult solid cancer patients between January 2012 and September 2015 with hypercalcemia. All encounters associated with HCM were identified using the ICD-9 code (275.42) for hypercalcemia. Encounters with other known causes of hypercalcemia were excluded. The co-primary outcomes were incidence of HCM and inpatient mortality. During the study period, 7,501,209 hospitalizations met our inclusion criteria. Approximately 1.7% ($n = 126{,}875$) of these hospitalizations were related to HCM. This corresponds to approximately 1 in 59 solid malignancy associated hospitalizations. The mean age of patients with HCM was 65.7 years; 49% were females; 69% were Caucasians; 73% had metastatic disease and 22% received a palliative care consult. When compared to those without HCM, those hospitalized with HCM had a significantly longer mean hospital length of stay (7.3 days vs. 5.6 days, $p < 0.001$), higher inpatient mortality (12.3% vs. 5.5%, adjusted OR 1.76 (95% CI 1.69–1.84), $p < 0{\cdot}0001$), and a greater likelihood of discharge to other facilities (27.4% vs. 16.2%, $p < 0.0001$). Although HCM accounts for < 2% of all hospitalizations in patients with solid cancer, those with HCM display higher mortality than those without HCM.

Keywords Hypercalcemia of malignancy · Solid cancer · Inpatient mortality · National inpatient sample

Introduction

Hypercalcemia is one of the most common metabolic complications of malignancy. Hypercalcemia of malignancy (HCM) is an oncologic emergency and in severe cases can be life-threatening if untreated [1]. The incidence of HCM varies greatly and has been reported in up to 30% of cancer patients at some point during the course of their disease [2]. It is most commonly associated with multiple myeloma, lung cancer, breast cancer, and renal cell cancer [3, 4]. Humoral HCM due to secretion of parathyroid hormone-related protein is the most common mechanism of HCM and is associated with up to 80% of cases. Another mechanism of HCM includes local osteolytic hypercalcemia due to bone metastasis [2]. HCM carries a very poor prognosis with an estimated overall median survival of 30 days despite treatment for hypercalcemia, but does improve if specific anti-cancer treatment available [5]. A more recent study [6] with a cohort of 4874 cancer patients with hypercalcemia from 482 hospitals calculated an in-hospital mortality rate of 6.8%.

We aimed to describe the incidence of HCM-associated hospitalization in recent years and analyze HCM-associated in-hospital mortality using a national inpatient database.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12032-019-1315-8) contains supplementary material, which is available to authorized users.

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Published online: 16 September 2019

Materials and methods

Data source

We used the National Inpatient Sample (NIS) database for this study. We analyzed data from January 2012 to September 2015 (i.e., before the implementation of ICD-10 codes). The NIS is the largest publicly available all-payer, inpatient healthcare database in the USA developed through a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ) [7]. The NIS is a random 20% sample of inpatient discharges from U.S hospitals. Unweighted, it contains data from more than 7 million hospitalization each year. Weighted, it comprises more than 35 million annual hospitalization nationally.

The NIS data are organized such that each observation in the sample represents a unique hospitalization with information on more than 100 clinical characteristics: patient demographics (e.g., age, sex, race, median income for ZIP code), hospital characteristics (e.g., ownership, size, teaching status, census region and division), primary and up to 29 secondary diagnoses as well as 15 procedures as administrative codes, Diagnosis-Related Group codes for disease severity, discharge status and disposition, total charges, and length of stay. No major changes in NIS sampling methodology occurred during the study period.

Study population and methodology

We identified all hospitalizations among adult patients (age $\geq$ 18 years) with diagnoses of solid cancer between January 2012 and September 2015 (Fig. 1). All ICD-9 codes used to identify the study population are provided as supplementary appendix A. Since there is no specific ICD-9 code for malignancy associated hypercalcemia, we excluded all encounters that had concomitant diagnoses or procedures known to cause hypercalcemia. The remaining encounters with assigned ICD-9 code for hypercalcemia (275.42) were assumed to be malignancy related. We opted to include encounters with either a primary or secondary diagnosis of hypercalcemia as this diagnosis is very unlikely to be a chronic comorbid condition. We also excluded encounters with a concomitant hematological malignancy or missing mortality data.

We made our best attempt to adhere to NIS best practices as described by the Healthcare Cost and Utilization Project and Khera et al. [8]. This study was deemed exempt from review by the Institutional Review Board of University of Louisville School of Medicine. All encounters were

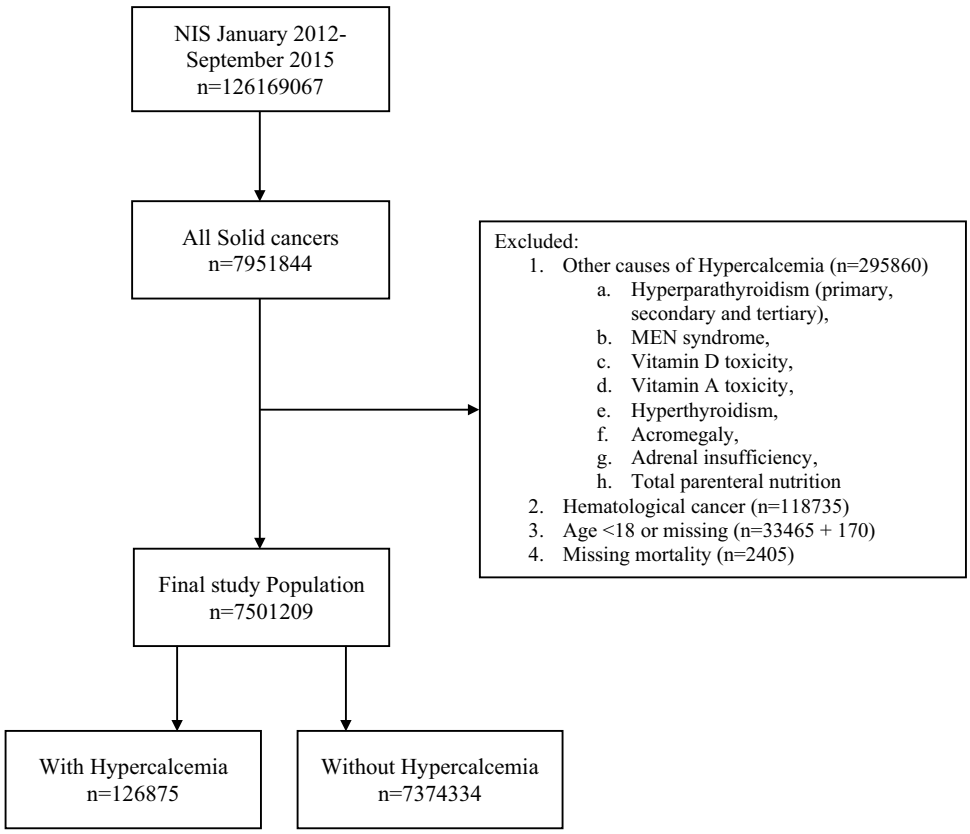

Fig. 1 Flow diagram of study population

categorized into two comparison groups, i.e., with or without HCM.

Outcomes

The co-primary study outcomes were (1) the incidence of HCM-associated hospitalizations and (2) the rate of inpatient mortality associated with HCM. Secondary outcomes included length of stay, total hospital charges, discharge location, palliative consult, and factors associated with inpatient mortality.

Statistical analyses

We performed a survey-weighted analysis using the SVY command to account for stratification and clustering of data. Univariate analysis was performed using Pearson's Chi-squared test for categorical variables and Student's *t* test for continuous variables. Univariate logistic regression analysis was used to calculate unadjusted odds ratios (OR) for outcomes followed by multivariate logistic regression analysis to adjust for potential confounding variables. Patients with missing information for any variable in the regression analyses were excluded. All p values were two-sided, with an alpha of 0.05 as the threshold for statistical significance. Statistical analyses were performed using Stata Version 15 (Stata Corporation, College Station, TX).

Results

This study analyzed 7,501,209 hospitalizations in patients diagnosed with solid cancer. Among these hospitalizations, 15,370 (0.2%) were related to a primary diagnosis of hypercalcemia, while 111,505 (1.5%) were related to a secondary diagnosis of hypercalcemia. Patient demographic and clinical characteristics are described in Table 1. Forty-nine percent of the study population were females. The presence of HCM among hospitalizations was highest in lung cancer (29.5%), followed by breast cancer (10.3%) and renal/bladder cancer (10.2%).

Hospitalizations with HCM were compared to those without HCM. Age and sex distribution were not significantly different between the groups. African-American were more strongly represented in the HCM group compared to non-HCM group (19.6% vs. 12.9%, respectively; OR 1.39, 95% CI 1.34–1.44; $p < 0.001$). Comorbid conditions were also more common in the HCM group, with an average Charlson comorbidity index of 6 versus 4.8 in non-HCM group ($p < 0.001$). Metastatic disease was more likely in the HCM group compared to non-HCM group (73% vs. 44%, respectively; OR 2.94, 95% CI 2.84–3.05; $p < 0.001$). Those with HCM were also more likely to receive a palliative care consult than those without (21.7% vs 8.7%, respectively; $p < 0.001$).

The all-cause in-hospital crude mortality rate for the HCM group was 12.3% versus 5.5% in non-HCM group ($p < 0.001$). Patients with HCM displayed a significantly higher odds of all-cause mortality after adjusting for age, sex, race, comorbidities, protein calorie malnutrition, type of cancer, and metastatic disease, with an adjusted odds ratio of 1.76 (95% CI 1.68–1.84). Predictors of in-hospital mortality among patients hospitalized with HCM are described in Table 2. Age, sex, insurance, metastatic disease, protein calorie malnutrition, cardiopulmonary arrest, and need for mechanical ventilation were significantly associated with worse outcomes, while patients who received inpatient chemotherapy were significantly associated with better outcomes.

Hospitalizations in patients with HCM experienced a significantly longer mean length of stay (LOS) than those without HCM (7.3 days vs. 5.6 days, respectively; $p < 0.001$) and were discharged more frequently to skilled nursing, rehabilitation, or other facilities that included inpatient hospice unit than those without HCM (27.4% vs. 16.2%, $p < 0.001$). Overall hospitalization cost was also higher for the HCM group at a mean of $59,546 compared to a mean cost of $54,641 among those without HCM ($p < 0.001$).

Discussion

This is one of the largest studies to evaluate demographics, clinical characteristics, and outcomes associated with the care of solid cancer patients with HCM in the United States. These real-world data further our understanding of hospitalizations related to HCM.

We found that HCM accounts for 1.7% of all hospitalizations in patients with solid cancer and is associated with worse outcomes. We reported a higher overall in-hospital mortality among patients with solid malignancy (12.3%) in contrast to a previous study noting a mortality rate of 6.8% [6]. A likely explanation for this difference is that the previous study included patients with multiple myeloma (24% of sample population) who possess an overall lower mortality risk.

Overall, HCM is associated with poor survival; yet, some studies have demonstrated survival improvement upon chemotherapy administration in treatment naïve patients and breast cancer patients [5, 9]. Our study also shows improved survival with the receipt of inpatient chemotherapy. It is important to state that this is inpatient survival. Patients who received inpatient chemotherapy were likely younger with good performance status, fewer comorbidities, and treatment naïve.

Table 1 Patient demographic and clinical characteristics

	No hypercalcemia $n=7,374,334$	Hypercalcemia $n=126,875$	*P* value
Age, mean (years)	65.7	65.7	0.95
Female	48.9	49.3	0.26
Race			< 0.001
White	73.1	68.7	
Black	12.9	19.6	
Hispanic	7.8	6.7	
Other	6.1	5	
Insurance			< 0.001
Medicare	55.6	54.8	
Medicaid	10.2	14.4	
Private	28.9	24.5	
Other/self-pay	5.3	6.3	
Total number of comorbidities, mean	4.8	6	< 0.001
Hospital setting			< 0.001
Rural	8.3	9.1	
Urban non-teaching	27.6	29.8	
Urban teaching	64	61.1	
Hospital region			< 0.001
Northeast	21.1	20.2	
Midwest	22.9	22.8	
South	37.6	39.6	
West	18.5	17.4	
Type of cancer			
Lung	19.3	29.5	< 0.001
Breast	8.7	10.3	< 0.001
Colorectal/anal	11.7	3.8	< 0.001
Prostate	9.6	3.9	< 0.001
Head and neck	3.8	5.2	< 0.001
Pancreatic	4.4	2.8	< 0.001
Esophagus/gastric	3.6	2.7	< 0.001
Liver/biliary tract	3.4	3	< 0.001
Bone/connective tissue	1.9	1.3	< 0.001
Melanoma	0.9	0.6	< 0.001
Kidney/bladder	7.9	10.2	< 0.001
Central nervous system	2.7	0.6	< 0.001
Male genital	0.4	0.4	0.387
Female genital	6.6	4.8	< 0.001
Other	16.9	22.8	< 0.001
Metastatic cancer	44	73.3	< 0.001
Mechanical ventilation use	3.6	4.7	< 0.001
Renal disease	10.5	14	< 0.001
Inpatient chemotherapy	3.8	4.8	< 0.001
Palliative consult	8.7	21.7	< 0.001
Protein calorie malnutrition	9.3	19.7	< 0.001
Total hospital charge (US dollars)			< 0.001
< 49 K	63.7	61.4	
55–99 K	22.1	22.4	
> 100 K	14.2	16.2	

Table 2 Predictors of mortality among patients hospitalized for hypercalcemia of malignancy

Characteristics and complications	Odds ratio (95% confidence interval)	*p* value
Age	1.01 (1.00,1.02)	< 0.001
Sex (Female)	0.84 (0.77, 0.93)	0.001
Race		
White	Reference	0.064
Black	0.89 (0.79, 1.00)	0.498
Hispanic	0.93 (0.77, 1.12)	0.131
Asian	1.21 (0.94, 1.57)	0.294
Other	1.14 (0.88, 1.47)	
Insurance		
Medicare	Reference	0.272
Medicaid	1.08 (0.93, 1.26)	< 0.001
Private	1.27 (1.13, 1.44)	< 0.001
Self-pay/other	1.74 (1.46, 2.07)	
Charlson comorbidity index		
< 3	Reference	0.522
> 3	1.06 (0.87, 1.29)	
Type of facility		
Rural	Reference	0.049
Urban non-teaching	0.84 (0.71, 0.99)	0.156
Urban teaching	0.89 (0.76, 1.04)	
Metastatic disease	1.73 (1.52, 1.97)	< 0.001
Protein calorie malnutrition	1.35 (1.22, 1.49)	< 0.001
Inpatient chemotherapy	0.72 (0.58, 0.89)	0.003
Mechanical ventilation	12.07 (10.50, 13.87)	< 0.001
Cardiopulmonary arrest	15.06 (8.62, 26.32)	< 0.001

Another important finding from this study is the frequency of palliative care consults in this population. Although it is known that HCM has a mortality risk of 50% within a month of diagnosis and is mostly associated with metastatic disease, only 22% of patients received a palliative care consult. Integration of palliative care in cancer patients has shown to improve patient quality of life [10], while inpatient palliative care consultation can help decrease readmission rates and provide an overall increase in supportive measures following discharge [11].

Limitations

There are several limitations to this study, despite the large power afforded by the NIS database. The NIS database is an inpatient database and is based on administrative coding. For this reason, it is not possible to accurately determine all patients with hypercalcemia as mild asymptomatic hypercalcemia was likely not coded. Also, the severity of hypercalcemia is not recorded in the database. Additionally, cancer histology and disease stage are well-established prognostic factors, but specific information was not available to control for these potential confounders. Furthermore, our study is subject to potential issues common in retrospective studies including selection bias; for instance, our study cohort likely selected for the most symptomatic HCM patients, as many patients diagnosed with mild to moderate HCM may be treated on an outpatient basis. Lastly, we were unable to differentiate re-hospitalizations, and an accurate estimate of the total patient burden could not be ascertained due to the nature of the NIS database.

Conclusions

This study is one of the largest studies using retrospective national data to describe clinical characteristics and outcomes related to HCM. HCM accounts for < 2% of all hospitalizations in patients with solid cancer and has a higher inpatient mortality than hospitalizations without HCM. Age, sex, insurance, metastatic disease, protein calorie malnutrition, cardiopulmonary arrest, and the need for mechanical ventilation were associated with poor survival. Despite improvements in cancer care and a decline in US cancer death rates, hypercalcemia remains a strong predictor of mortality in cancer patients.

Compliance with ethical standards

Conflict of interest All authors declare that they have no competing interest.

Ethical approval This study was a retrospective study using de-identified information from a database and did not directly interact with human participants.

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