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ORIGINAL ARTICLE

Analysis of hypercalcemia in hospitalized patients in Spain from 2001 through 2015

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KEYWORDS
Hypercalcemia;
Calcium metabolism disorders;
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Routinely collected health data

Abstract
Introduction: Few studies have explored the characteristics of hospitalized patients with hypercalcemia. Our goal was to analyze clinical–epidemiological features, mortality, and incidence of hypercalcemia in Spanish adult inpatients.
Materials and methods: We conducted a retrospective study using Spain's nationwide hospital database (''Conjunto Mínimo Básico de Datos Hospitalización'', CMBD-H), analyzing all hospital discharges from 2001 through 2015. Hypercalcemia was defined according to ICD-9-CM code 275.42. We examined causes, sex, median age, length of stay, and in-hospital mortality. Annual rates, adjusted for age and sex, were analyzed too.
Results: A total of 41,103 cases of hypercalcemia were analyzed out of 59,978,703 hospital discharges. Median age was 70 (interquartile range [IQR], 59–79), with 51.3% males. Internal Medicine had the most discharges (32.8%). Hypercalcemia was the leading cause in 11.4% of cases. Most common etiologies were cancer (83.8%) and hyperparathyroidism (15.1%). Neoplasms were more prevalent in males and older patients. Mean incidence was 0.7/1000 admissions, with a 7.1% annual growth rate. The overall in-hospital mortality rate was 27.1%, which remained unchanged over the study period. Factor s associated with mortality included increasing age (OR, 1.01; 95% CI, 1.01–1.02), male sex (1.60; 1.53–1.68), emergency admission (1.43; 1.34–1.52), hypercalcemia as main diagnosis (1.89; 1.74–2.06), and neoplasm (5.24; 4.92–5.58).

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Conclusions: This is the largest and most comprehensive general study on in-hospital hypercalcemia conducted to this date. The rate of hypercalcemia in hospitalized patients is increasing, likely due to the growing number of cancer inpatients. Hypercalcemia was associated with high mortality.

PALABRAS CLAVE
Hipercalcemia;
Trastornos metabólicos del calcio;
Síndromes paraneoplásicos;
Hiperparatiroidismo;
Datos de salud recopilados rutinariamente

Análisis de la hipercalcemia en los pacientes hospitalizados en España entre 2001-2015

Resumen
Introducción: Pocos estudios han profundizado en la exploración de las características de los pacientes hospitalizados con hipercalcemia. Nuestro objetivo fue analizar las características clínicas y epidemiológicas, mortalidad e incidencia de la hipercalcemia en los pacientes adultos hospitalizados en España.
Materiales y métodos: Realizamos un estudio retrospectivo utilizando la base de datos nacional de los hospitales de España (conjunto mínimo básico de datos hospitalización [CMBD-H]), analizando todos los ingresos desde 2001 hasta 2015. La hipercalcemia se definió según el código ICD-9-CM 275.42. Analizamos las causas, el sexo, la media de edad, la duración del ingreso hospitalario y la mortalidad intrahospitalaria. También, las tasas anuales, ajustadas por edad y sexo.
Resultados: Se analizaron un total de 41.103 casos de hipercalcemia procedentes de 59.978.703 ingresos. La mediana de edad fue de 70 años (rango intercuartílico [RIC]: 59-79) siendo el 51,3% de la muestra, varones. Medicina interna tuvo el mayor número de ingresos (32,8%). La hipercalcemia fue la causa principal en el 11,4% de los casos. Las etiologías más comunes fueron cáncer (83,8%) e hiperparatiroidismo (15,1%). Las neoplasias fueron más prevalentes entre los varones y en los pacientes de edad avanzada. La incidencia media fue de 0,7/1.000 ingresos, con una tasa de crecimiento anual del 7,1%. La tasa global de mortalidad intrahospitalaria fue del 27,1%; tasa que se mantuvo sin cambios durante el período de estudio. Los factores asociados a la mortalidad incluyeron la edad avanzada (OR: 1,01; IC 95%: 1,01-1,02), el sexo masculino (1,60; 1,53-1,68), los ingresos de urgencias (1,43; 1,34-1,52), la hipercalcemia como diagnóstico principal (1,89; 1,74-2,06) y las neoplasias (5,24; 4,92-5,58).
Conclusiones: Este es el estudio general más grande y completo jamás realizado sobre hipercalcemia intrahospitalaria. La tasa de hipercalcemia en los pacientes hospitalizados va en aumento, probablemente por el cada vez mayor número de pacientes oncológicos. La hipercalcemia se asoció a una alta tasa de mortalidad.

Introduction

Hypercalcemia is characterized by a plasma calcium concentration of >10.2 mg/dL (2.5 mmol/L), resulting from an imbalance between calcium intake and excretion. Various conditions such as neoplasms, hyperparathyroidism, and vitamin D intoxication can lead to hypercalcemia, and its severity can vary from asymptomatic to severe neurological and cardiac signs, depending on the level of calcemia.[1] There have been relatively few studies that have investigated the clinical and epidemiological characteristics of hospitalized patients with hypercalcemia. Furthermore, most of the available studies were conducted in the 20th century and not in our particular setting.

The primary objective of this study was to provide a description of the demographic and clinical features of hospitalized patients with hypercalcemia in Spain from 2001 through 2015 including an analysis of age and gender distribution, etiological factors, associated comorbidities, and the responsible departments overseeing their care. As a secondary objective, we aimed to estimate the incidence and associated mortality of hypercalcemia in the hospital setting during this period.

Materials and methods

Design, location, and participants

The present study was conducted as a descriptive, cross-sectional, observational, and retrospective research, utilizing the ''Conjunto Mínimo Básico de Datos

Hospitalización'' (CMBD-H) database, which is maintained by the Spanish Ministry of Health, and includes information on all hospital discharges from the National Health System's acute care facilities. The database provides details on patient characteristics, including age, sex, residence, admissions, as well as diagnoses and procedures that occurred during hospitalization. All data from the CMBD-H database were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

The present study included an analysis of discharge records from 2001 through 2015. Patients aged 15 years or older with a diagnosis of hypercalcemia, as defined by the ICD-9-CM code 275.42, were selected for analysis, while duplicate cases were excluded. Hypercalcemia was categorized as primary if it was the main cause of admission, and as secondary if it occurred and/or was detected during the hospital stay but was not the direct cause of admission.

Variables

The variables from the CMBD-H database were recoded and categorized based on their corresponding diagnoses and procedures. For a comprehensive list of these variables along with their descriptions, see supplementary data.

Data sources

Data for this study were retrieved from the CMBD-H database, which was provided by the Institute of Health Information of the Spanish Ministry of Health. To estimate the annual incidence rates, population data as of July 1st for each studied year were obtained from the National Statistics Institute.

Statistical methods

To identify and exclude duplicate cases, we used the following variables: sex, date of birth, region of residence, and type of hospital. We initially conducted a descriptive analysis of the study variables. Qualitative variables were expressed as absolute and relative frequencies while the continuous ones as mean with standard deviation (SD) if they followed a normal distribution, or as median with interquartile range (IQR) if they did not. The Kolmogorov–Smirnov test was used to verify the normal distribution of quantitative variables.

The study used a significance level (alpha) of 0.05 and two tails for all tests. Cases with missing values for certain variables were excluded from the analysis. The chi-square test or Fisher's exact test were used to determine statistically significant associations between qualitative variables based on whether the expected percentages were <5 or >20%. The Mann–Whitney *U* test, Student's *t*-test, or the Kruskal–Wallis test were used to determine statistically significant associations between qualitative and quantitative variables based on the number of groups and normality criteria.

Logistic regression models were used to analyze the effects of variables on different events. The validity of multivariate models was verified using the Hosmer–Lemeshow test and the area under the receiver operating characteristic curve (AUC-ROC). To qualify the magnitude of the effect of statistically significant associations in tests with $p < 0.1$, Cohen's *d* was applied to the odds ratio (OR).[2] In the analysis of incidence, the compound annual growth rate (CAGR) was estimated as the geometric mean of individual changes from period to period.

The statistical analysis was performed using IBM® SPSS® Statistics 26 software. The recommendations of the RECORD statement for observational studies using routinely collected health data[3] were followed while preparing this manuscript.

Ethical aspects

The study was approved by the Provincial Research Ethics Committee of Málaga, Spain. Data were anonymized before being provided to the researchers.

Results

General cohort study

A total of 41,103 unique cases were analyzed after excluding duplicate records. Detailed characteristics are shown in Table 1. The median age of the cohort was 70 years (IQR, 59–79), and there was a slightly higher proportion of males (51.3%). Most cases were admitted to Internal Medicine and related areas (32.8%), followed by Medical and Radiation Oncology (15.4%), Hematology (7.1%), Nephrology (4.6%), General Surgery (2.8%), Palliative Care (2.4%), Endocrinology (1.9%), Pulmonology (1.6%), Gastroenterology (1.1%), and Neurology (1.1%). The remaining cases (29.1%) belonged to other minority services (<1%) or were uncoded. In 81.4% of cases, the type of admission was urgent. Hypercalcemia was the main diagnosis in 11.4% of cases; this means that it was the diagnosis that the attending physician indicated as primary in the discharge report. The median length of stay was 10 days (IQR, 5–17), and the median cost of admission, €4,184 (IQR, 3.326–5.580).

Of the 41,103 unique cases analyzed, 77.5% had, at least, 1 coded diagnosis related to hypercalcemia: 73.5% had 1 diagnosis, 3.9% had 2 diagnoses, and 0.1% had 3 or 4 diagnoses. In the remaining 22.5% of cases, no coded diagnosis related to hypercalcemia was ever identified, and the origin of hypercalcemia could not be determined. Among cases with any coded related diagnosis, neoplasms were the most frequent (83.8%), followed by hyperparathyroidism (15.1%), thyrotoxicosis (2.1%), parenteral nutrition (1.6%), sarcoidosis (0.8%), rhabdomyolysis (0.5%), adrenal insufficiency (0.4%), vitamins A–D intoxication (0.4%), thiazide diuretic intoxication (0.3%), and lithium and theophylline intoxications (<0.1%). The most common coded comorbidities were acute kidney injury (19.1%), delirium (6.3%), nephrolithiasis (2%), phosphorus disorders (1.1%), magnesium disorders (0.9%), and hypocalcemia (0.4%). None of these cases had a coded procedure for renal replacement therapy.

The study found an in-hospital mortality rate of 27.1%. Primarily, a univariate logistic regression analysis was performed using potentially relevant variables available in the

Table 1 Characteristics of the patients included in the cohort.

Median age, years (IQR)	70 (59–79)
Sex, *n* (%)	
Male	21,084 (51.3)
Female	20,017 (48.7)
Department of admission, *n* (%)	
Internal Medicine and related areas	13,473 (32.8)
Oncology (Medical and Radiation)	6331 (15.4)
Hematology	2924 (7.1)
Nephrology	1895 (4.6)
General Surgery	1113 (2.8)
Palliative Care	970 (2.4)
Endocrinology	762 (1.9)
Neumology	645 (1.6)
Gastroenterology	534 (1.3)
Neurology	471 (1.1)
Others and non-coded	11,965 (29.1)
Coded etiologies, *n* (%)	
Neoplasm	26,706 (83.8)
Hyperparathyroidism	4824 (15.1)
• Primary	2773 (8.7)
• Secondary	576 (1.8)
• Tertiary	1781 (5.6)
Thyrotoxicosis	678 (2.1)
Parenteral nutrition	494 (1.6)
Sarcoidosis	269 (0.8)
Rhabdomyolysis	149 (0.5)
Adrenal insufficiency	139 (0.4)
Vitamins A–D intoxication	114 (0.4)
Thiazide diuretic intoxication	84 (0.3)
Lithium intoxication	7
Theophylline intoxication	2
No. of coded etiologies, *n* (%)	
One	30,198 (73.5)
Two	1600 (3.9)
Three	57 (0.1)
Four	2
None	9246 (22.5)
In-hospital mortality, *n* (%)	11,132 (27)

IQR: interquartile range.

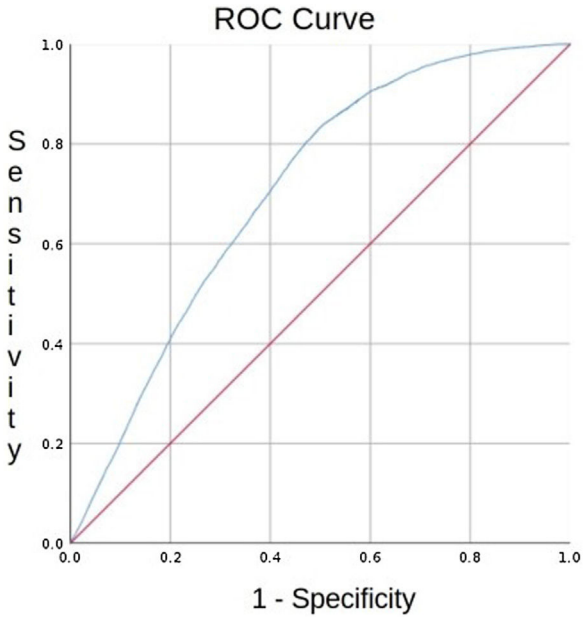

Figure 1 Receiver operating characteristic (ROC) curve of the multivariate logistic regression model used to analyze the effects of various variables on the odds of in-hospital mortality.

database to examine their effects on in-hospital mortality. Since all variables exhibited a statistically significant association with mortality, they were used to construct the multivariate regression model. Significant associations were seen with increasing age (each year associated with higher odds of mortality), male sex (higher odds), emergency admission type (higher odds), hypercalcemia diagnosis as primary diagnosis (higher odds), and presence of a coded diagnosis of neoplasm (higher odds). Further details of the analysis results are provided in Table 2, and the ROC curve is presented in Fig. 1.

Comparative study by sex

The complete comparative analysis between males and females is presented in Table 1 of the supplementary data. Statistically significant differences were reported in most

Table 2 Multivariate logistic regression model to study the effects of different variables on the probability of in-hospital mortality.

	OR	95% CI	*p*	ME
Diagnosis of neoplasm	5.24	4.92–5.58	<0.001	Moderate
Hypercalcemia as main diagnosis	1.89	1.74–2.06	<0.001	Small
Sex (male)	1.6	1.53–1.68	<0.001	Insignificant
Emergency admission	1.43	1.34–1.52	<0.001	Insignificant
Age (years)	1.014	1.012–1.016	<0.001	Insignificant

Backwards stepwise likelihood ratio method, correct classification of 72.8% of cases.
$R_2^{\text{Nagelkerke}} = 0.115–0.166$. Hosmer–Lemeshow test: $p < 0.001$.
ROC curve: AUC 0.708 (95% CI, 0.703–0.714); $p < 0.001$.

OR: odds ratio; CI: confidence interval; ME: magnitude of the effect (Cohen's *d*); ROC: receiver operating characteristic; AUC: area under the ROC curve.

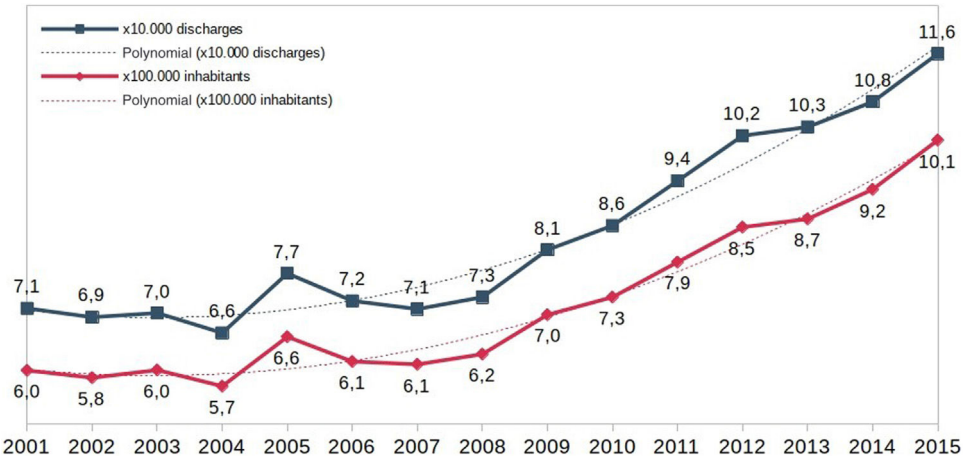

Figure 2 Annual incidence of hypercalcemia (population aged 15 years or older) in the national health system. Top line (blue) per 10,000 discharges, bottom line (red) per 100,000 inhabitants. General trends in dotted lines.

analyses performed. Males had a lower median age (67 years vs 71 years), a lower proportion of hypercalcemia coded as the primary diagnosis, a higher proportion of emergency admissions, a higher proportion of, at least, 1 coded etiology, a lower proportion of multiple coded etiologies, and a higher in-hospital mortality rate (33.7% vs 20%).

Relevant differences were reported between men and women in terms of the proportion of different etiologies for hypercalcemia. Specifically, men had a higher proportion of neoplasms vs women (75.5% vs 53.9%), while women had a higher proportion of coding for hyperparathyroidism (17% vs 6.7%), thyrotoxicosis, adrenal insufficiency, and intoxications with thiazide diuretics, vitamins A–D, and lithium. There were no statistically significant differences in the proportion of coded diagnoses of parenteral nutrition, sarcoidosis, and rhabdomyolysis between men and women.

Regarding neoplasms, a higher proportion of coding for lung, head and neck, GI tract, bladder, and kidney neoplasms was reported in men vs women. On the other hand, in women, a higher proportion of coding for breast, multiple myeloma, lymphoma, genital, endocrine, and uncoded neoplasms were reported vs men. No statistically significant differences were found in the proportion of coded diagnoses of hepatobiliary and pancreatic neoplasms and neuroendocrine tumors. Additionally, the proportion of multiple coded neoplasms was higher in men vs women.

Comparative study by age groups

The complete comparative analysis across different age groups (15–44 years, 45–64 years, and ≥65 years) is shown in Table 2 of the supplementary data. Statistically significant differences were reported in many of the analyses conducted. The 45–64 age group had a higher proportion of males, whereas the ≥65 age group had a higher proportion of females. Emergency admissions were more frequent in the ≥65 age group. The median length of stay and cost of admission increased progressively with age, and in-hospital mortality was significantly higher in the 45–64 years and ≥65 years age groups.

Regarding etiologies, neoplasms were more frequent in the 45–64 age group vs other groups. Breast and genitals neoplasms, lymphomas, hepatobiliary-pancreatic and endocrine system neoplasms were more widely reported in the 15–44 age group. Lung, head and neck, GI tract, and kidney neoplasms were more frequent in the 45–64 age group. Multiple myeloma and neoplasms of the bladder and prostate were more common in the ≥65 age group. Hyperparathyroidism, thyrotoxicosis, parenteral nutrition, sarcoidosis, adrenal insufficiency, and rhabdomyolysis were more frequent in the 15–44 age group. Intoxications with vitamins A–D and thiazide diuretics were more common in the ≥65 age group. The 15–44 age group had a higher proportion of cases without a coded diagnosis related to the development of hypercalcemia.

Annual incidence study

In our series, the overall prevalence of hypercalcemia was 0.07% among all discharges. The annual incidence of hypercalcemia in hospitalized patients is shown in Fig. 2. The incidence remained relatively stable between from 2001 through 2008 at around 7.1 cases per 10,000 discharges, with an CAGR of 0.6%. Starting in 2008, an upward trend was observed, reaching 11.6 cases per 10,000 discharges in 2015, which is representative of a CAGR of 7.1% in this period. The graph per 100,000 inhabitants follows a similar trend. Using 2015 as the reference year, the incidence per 100,000 inhabitants was 1.3 cases among 15–44-year-olds, 8.7 cases among 45–64-year-olds, and 30.6 cases in those over 65 years old.

When looking at the incidence by sex, we saw that the incidence in men was higher vs women throughout the entire period, although the difference narrowed in recent years (see Fig. 1 of the supplementary data).

Analyzing the annual in-hospital mortality rate of patients with hypercalcemia per 10,000 discharges (see Fig. 3), an annual increase of 1% was reported from 2001 through 2008 and 6% from 2008 through 2015 (3.3% overall). However, when calculated per 100 discharges with a coded diagnosis of hypercalcemia, the mortality rate remained

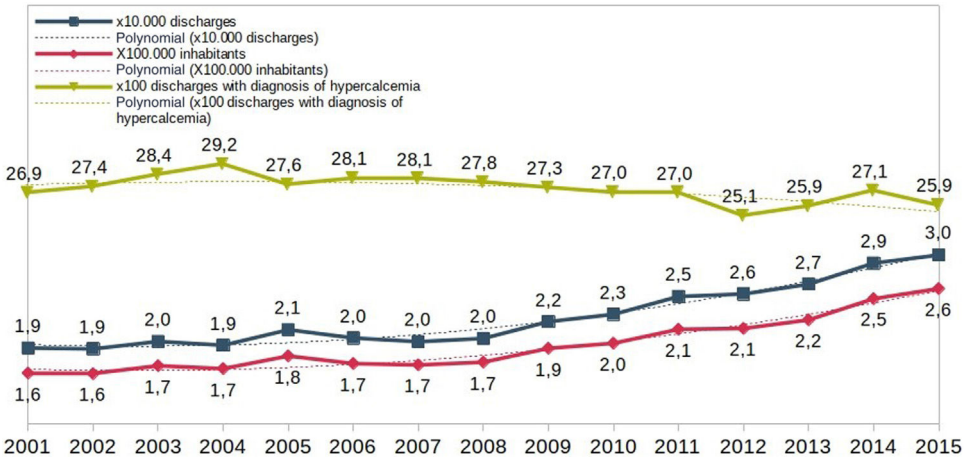

Figure 3 Annual in-hospital mortality rate of patients with hypercalcemia (population aged 15 years or older) in the national health system. Top line (green) per 100 discharges with coded diagnosis of hypercalcemia, middle line (blue) per 10,000 discharges, bottom line (red) per 100,000 inhabitants. General trends in dotted lines.

stable at around 27% with a slightly and non-significant downward trend (CAGR, −0.3%).

Discussion

This study of the Spanish national cohort of the CMBD-H is the largest general study published to this date on hospitalized patients with hypercalcemia. A similar study was conducted by Bhandari et al. in 2019,[4] using a US database analogous to the CMBD-H, which included 126,875 discharges but only studied hypercalcemia in non-hematologic cancer patients. Compared to 22 previously published series from 1981 through 2020,[5–26] along with another series of our own,[27] a slight male predominance was also seen. The incidence of hypercalcemia in the study population went from 0.071% up to 0.116% depending on the year. This is significantly lower than the one reported in the reviewed series: only 14 former studies reported an incidence estimate from 0.28% up to 7.5%, with a median of 1.28%. However, in our series mentioned above, the incidence was 0.13%, which is very similar to the incidence found in this study. Although the exact causes of the difference in incidence compared to former studies cannot be determined, it is likely due to differences in the populations studied and the methodologies used. The 15 years analyzed in the study exceeded the 13 years of the longest series.[14]

The Internal Medicine departments and related areas provided the highest number of discharges with the coded diagnosis of hypercalcemia. The proportion of discharges with hypercalcemia coded as the primary diagnosis was very small, most likely because this coding was assigned to the cause of hypercalcemia or to a different more relevant comorbidity during admission. As expected from former studies,[28] although neoplasms were the most frequent coded diagnoses, followed by hyperparathyroidism, the significant heterogeneity in methodologies and study populations across different studies makes direct comparisons impossible. We analyzed all coded types of hyperparathyroidism together because we saw a higher-than-expected frequency of coding for secondary (which can cause hypocalcemia)[29] and tertiary (rare and associated with advanced chronic kidney disease)[30] types. Furthermore, in some instances, multiple types were coded simultaneously, which suggests that numerous cases of primary hyperparathyroidism may have been incorrectly coded. Table 1 displays the detailed data for each type of hyperparathyroidism.

Although thyrotoxicosis, parenteral nutrition, and adrenal insufficiency represented a significant proportion of other diagnoses, it is likely that in many cases (except for those that were the only possible diagnosis), they were just ''innocent bystanders'', as the development of hypercalcemia associated with these disorders is not a very common finding.[1] Regarding sarcoidosis, rhabdomyolysis, and intoxications with vitamins A–D and thiazide diuretics, it is likely that in most cases they were responsible for hypercalcemia since they are rare diseases classically related to the development of hypercalcemia though.[28] Associated comorbidities are likely to be undercoded, since calcium disorders are frequently linked with disorders of phosphorus and magnesium.[1]

The multivariate regression model on in-hospital mortality showed interesting results. Although its discrimination ability is moderate (around 0.71), it is reasonably accurate considering it was developed from a database designed for other purposes. Findings are consistent with clinical knowledge, indicating a moderate increased risk of mortality for patients with a coded diagnosis of neoplasm. Hypercalcemia as the primary diagnosis posed a small increased risk, likely because it represented cases with more severe hypercalcemia, yet we cannot confirm this with certainty. The increased risk associated with male sex, due to a higher proportion of neoplasm cases, was adjusted in the multivariate analysis, making it possible that although neoplasms in men were more fatal vs women, the effect size was minimal. Similarly, the increased risks associated with emergency admissions, which generally represent more severe cases than scheduled admissions, and older age were statistically significant but of a magnitude too small to have clinical relevance. There are many other factors that may have contributed to mortality; however, due to database limitations and the added complexity that would come with

a broader analysis, coupled with the acceptable utility of the model presented, we have not considered expanding the variables to include those not originally included in the study initial protocol.

The comparative study by sex showed a significant difference in the proportion of neoplasm cases, which were more common in men, which showed in a higher in-hospital mortality rate in men too. On the other hand, hyperparathyroidism and thyrotoxicosis were more frequently diagnosed in women, which is consistent with previous research. Therefore, the study results are not surprising in this regard.

The studies on the annual incidence of hypercalcemia suggest an increasing trend, particularly from 2008 onwards. This trend is observed both in terms of the proportion of hospital discharges and the general population and could be associated with the increased number of admissions reported in cancer patients. When analyzed by sex and age groups, the growing trend is more pronounced in women and in the age group $\geq$65 years. Similarly, mortality analysis shows an increase from 2008 in relation to total discharges and the general population, without an increase in mortality relative to discharges with a coded diagnosis of hypercalcemia, which suggests that the increased overall mortality is not due to a higher mortality which could be attributed to hypercalcemia *per se* or to poorer clinical management, but rather is associated with the increased coding of the hypercalcemia diagnosis, which rises in relation to other diagnoses.

Limitations and strengths

The study principal strengths reside in its substantial sample size and the prolonged duration of the study period, enabling descriptions and analyses that are unattainable with small samples gathered individually from hospital centers. Additionally, it facilitates the estimation of the incidence of rare causes and temporal trends of hypercalcemia. However, it is essential to acknowledge that studies utilizing administrative databases like CMBD-H also come with several notable limitations due to their design:

- Since there is no unique identifier for each individual, it is not possible to make sure that there are no repeated cases in the analysis, or that cases labeled as repeated have been excluded when they have not. To minimize the risk of duplication, we excluded cases that coincided in terms of sex, date of birth, region of residence, and type of hospital.
- Data reliability depends on the correct registration of diagnoses and procedures in discharge reports, and their subsequent adequate coding according to ICD-9-CM, which means that in many cases, information is lost because it is not recorded or coded properly. An example of this limitation is that in 22.5% of the cases, no coded diagnosis was ever found to explain the origin of hypercalcemia.
- The database does not provide information on the characteristics of the coded diseases to know their phenotypes, analytical values, etc. Therefore, we cannot know the real value of serum calcium in the included cases or confirm if they really had hypercalcemia.
- A causal relationship between hypercalcemia and coded related diagnoses cannot be established. In cases with a single coded diagnosis, it can be assumed with relative certainty that it was the cause of hypercalcemia, yet in cases with two or more diagnoses, it is impossible to verify.
- Only in-hospital mortality is recorded. It is not possible to know mortality in outpatient settings or emergency services.
- The study concluded in 2015, as the database format changed in 2016 to the Register of Specialized Care (RAE-CMBD), which utilized ICD-10 coding for diagnoses and procedures, and modified certain variables. These changes made it challenging to compare data from before and after 2016.

Conclusions

As far as we know, to this date, this study, based on the Spanish national cohort of the CMBD-H, represents the largest and most comprehensive general research on hospitalized patients with hypercalcemia. Despite the inherent limitations of administrative databases, it provides crucial insights into the clinical–epidemiological characteristics, as well as the temporal trends in incidence and mortality. We saw an increasing trend in admissions with hypercalcemia during the study period, seemingly associated with the growing number of admission due to tumoral conditions, which emerged as the predominant cause. Over one-quarter of patients admitted with hypercalcemia succumb during their admission, with no significant changes being reported over time. Key factors associated with mortality include cancer, hypercalcemia as the primary cause of admission, emergency admission, male sex, and old age.

CRediT authorship contribution statement

G.R.L. conceived the study, analyzed and interpreted the data, drafted the manuscript, approved the final version, and agreed to be made accountable for all aspects of the work.

A.R.C. and R.G.H. contributed substantially to data interpretation, critically reviewed the draft of the manuscript, approved its final version, and agreed to be made accountable for all aspects of the work.

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Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.endinu.2024.08.005.

References

1. Walker MD, Shane E. Hypercalcemia: a review. JAMA. 2022;328:1624, http://dx.doi.org/10.1001/jama.2022.18331.
2. Chen H, Cohen P, Chen S. How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. Commun Stat Simul Comput. 2010;39:860–4, http://dx.doi.org/10.1080/03610911003650383.
3. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12:e1001885, http://dx.doi.org/10.1371/journal.pmed.1001885.
4. Bhandari S, Kumar R, Tripathi P, Chan A, Mudra S, Redman R. Outcomes of hypercalcemia of malignancy in patients with solid cancer: a national inpatient analysis. Med Oncol. 2019;36:90, http://dx.doi.org/10.1007/s12032-019-1315-8.
5. Fisken RA, Heath DA, Somers S, Bold AM. Hypercalcaemia in hospital patients. Clinical and diagnostic aspects. Lancet. 1981;1:202–7, http://dx.doi.org/10.1016/s0140-6736(81)90071-4.
6. Harrop JS, Bailey JE, Woodhead JS. Incidence of hypercalcaemia and primary hyperparathyroidism in relation to the biochemical profile. J Clin Pathol. 1982;35:395–400, http://dx.doi.org/10.1136/jcp.35.4.395.
7. Finnis WA, Cohanim M, Yendt ER. Unsuspected hypercalcemia among adults in hospital. Can Med Assoc J. 1981;125:561–4.
8. Burkhardt E, Kistler HJ. Hypercalcemia in hospitalized patients. Diagnostic and prognostic aspects. Schweiz Med Wochenschr. 1981;111:2017–23.
9. Rajathurai A, Cove-Smith R. Hypercalcaemia in Cleveland: a hospital-based survey. J R Soc Med. 1984;77:742–6, http://dx.doi.org/10.1177/014107688407700906.
10. Blomqvist CP. Malignant hypercalcemia – a hospital survey. Acta Med Scand. 1986;220:455–63, http://dx.doi.org/10.1111/j.0954-6820.1986.tb02795.x.
11. Dent DM, Miller JL, Klaff L, Barron J. The incidence and causes of hypercalcaemia. Postgrad Med J. 1987;63:745–50, http://dx.doi.org/10.1136/pgmj.63.743.745.
12. Diamond TH, Botha JR, Vermaak WJ, Kalk WJ. Hypercalcaemia in the Johannesburg Hospital. Differential diagnosis and physician awareness of primary hyperparathyroidism. S Afr Med J. 1987;72:113–5.
13. Morlock G, Cadène C. Prevalence of hypercalcemia in adults in a hospital milieu. 1-Year systematic survey. Rev Rhum Mal Osteoartic. 1988;55:723.
14. Gupta CM. Evaluation and aetiopathogenesis of hypercalcaemia. A study of 89 patients. J Assoc Physicians India. 1990;38:337–9.
15. Shek CC, Natkunam A, Tsang V, Cockram CS, Swaminathan R. Incidence, causes and mechanism of hypercalcaemia in a hospital population in Hong Kong. Q J Med. 1990;77:1277–85, http://dx.doi.org/10.1093/qjmed/77.3.1277.
16. Blind E, Raue F, Zisterer A, Kohl B, Ziegler R. Epidemiology of hypercalcemia. Significance of the determination of intact parathyroid hormone for differential diagnosis. Dtsch Med Wochenschr. 1990;115:1739–45, http://dx.doi.org/10.1055/s-2008-1065219.
17. Cadène C, Morlock G. Value of routine laboratory tests in the etiologic diagnosis of hypercalcemias – advantage of differential analysis. Revue Du Rhumatisme. 1990;57:181–4.
18. Frølich A, McNair P, Transbøl I. Awareness of hypercalcaemia in a hospital population? Scand J Clin Lab Invest. 1991;51:37–41.
19. Walls J, Ratcliffe WA, Howell A, Bundred NJ. Parathyroid hormone and parathyroid hormone-related protein in the investigation of hypercalcaemia in two hospital populations. Clin Endocrinol (Oxf). 1994;41:407–13, http://dx.doi.org/10.1111/j.1365-2265.1994.tb02569.x.
20. Frølich A, Nielsen BF, Conradsen K, McNair P, Transbøl IB. Within-centre evaluation of hypercalcaemia discriminant functions 5 years after their development. Int J Biomed Comput. 1996;40:235–40, http://dx.doi.org/10.1016/0020-7101(95)01148-x.
21. Lee JK, Chuang MJ, Lu CC, Hao LJ, Yang CY, Han TM, et al. Parathyroid hormone and parathyroid hormone related protein assays in the investigation of hypercalcemic patients in hospital in a Chinese population. J Endocrinol Invest. 1997;20:404–9, http://dx.doi.org/10.1007/BF03347992.
22. Tokuda Y, Maezato K, Stein GH. The causes of hypercalcemia in Okinawan patients: an international comparison. Intern Med. 2007;46:23–8, http://dx.doi.org/10.2169/internalmedicine.46.6052.
23. Newman EM, Bouvet M, Borgehi S, Herold DA, Deftos LJ. Causes of hypercalcemia in a population of military veterans in the United States. Endocr Pract. 2006;12:535–41, http://dx.doi.org/10.4158/EP.12.5.535.
24. Lee C-T, Yang C-C, Lam K-K, Kung C-T, Tsai C-J, Chen H-C. Hypercalcemia in the emergency department. Am J Med Sci. 2006;331:119–23, http://dx.doi.org/10.1097/00000441-200603000-00002.
25. Lindner G, Felber R, Schwarz C, Marti G, Leichtle AB, Fiedler G-M, et al. Hypercalcemia in the ED: prevalence, etiology, and outcome. Am J Emerg Med. 2013;31:657–60, http://dx.doi.org/10.1016/j.ajem.2012.11.010.
26. Mousseaux C, Dupont A, Rafat C, Ekpe K, Ghrenassia E, Kerhuel L, et al. Epidemiology, clinical features, and management of severe hypercalcemia in critically ill patients. Ann Intensive Care. 2019;9:133, http://dx.doi.org/10.1186/s13613-019-0606-8.
27. Ropero-Luis G, López-Sampalo A, Sanz-Cánovas J, Ruiz-Cantero A, Gómez-Huelgas R. Characteristics of hospitalized patients with hypercalcemia in the province of Malaga: a longitudinal, retrospective, multicenter study. Rev Clín Esp (Engl Ed). 2023;223:486–92, http://dx.doi.org/10.1016/j.rceng.2023.07.009.
28. Tonon CR, Silva TAAL, Pereira FWL, Queiroz DAR, Junior ELF, Martins D, et al. A review of current clinical concepts in the pathophysiology, etiology, diagnosis, and management of hypercalcemia. Med Sci Monit. 2022;28:e935821, http://dx.doi.org/10.12659/MSM.935821.
29. Habas E, Eledrisi M, Khan F, Elzouki A-NY. Secondary hyperparathyroidism in chronic kidney disease: pathophysiology and management. Cureus. 2021;13:e16388, http://dx.doi.org/10.7759/cureus.16388.
30. Palumbo VD, Palumbo VD, Damiano G, Messina M, Fazzotta S, Lo Monte G, et al. Tertiary hyperparathyroidism: a review. Clin Ter. 2021;172:241–6, http://dx.doi.org/10.7417/CT.2021.2322.