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# Assessing the risk of hypercalcemic crisis in patients with primary hyperparathyroidism

Andrew J. Lowell, BA, Norah M. Bushman, BA, Xing Wang, PhD, Yue Ma, PhD, Susan C. Pitt, MD, MPHS, Rebecca S. Sippel, MD, David F. Schneider, MD, MS, and Reese W. Randle, MD\*

Department of Surgery, University of Wisconsin, Madison, Wisconsin

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### ABSTRACT

**Background:** Hypercalcemic crisis (HC) is a potentially life-threatening manifestation of primary hyperparathyroidism (PHPT). This study aimed to identify patients with PHPT at greatest risk for developing HC.

**Methods:** This retrospective cohort study included patients with a preoperative calcium of at least 12 mg/dL undergoing initial parathyroidectomy for PHPT from 11/2000 to 03/2016. We compared those with HC, defined as needing hospitalization for hypercalcemia, to those without HC.

**Results:** The study cohort included 29 patients (15.8%) with HC and 154 patients (84.2%) without HC. Demographics and comorbidities were similar between the groups. Patients with HC were more likely to have a history of kidney stones (31.0% versus 14.3%,  $P = 0.039$ ), higher preoperative calcium (median 13.8 versus 12.4 mg/dL,  $P < 0.001$ ), higher parathyroid hormone (PTH) (median 318 versus 160 pg/mL,  $P = 0.001$ ), and lower vitamin D (median 16 versus 26 ng/mL,  $P < 0.001$ ) than patients without HC. Cure rates with parathyroidectomy were similar, but nearly double the proportion of patients with HC had multigland disease (24.1 versus 12.3%,  $P = 0.12$ ). In multivariable analysis, higher preoperative calcium (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.1–2.5), higher PTH (OR 1.0, 95% CI 1.0–1.0), and kidney stones (OR 3.0, 95% CI 1.1–8.2) were independently associated with HC. A Classification and Regression Tree revealed that HC developed in 91% of patients with a calcium  $\geq 13.25$  mg/dL and a Charlson Comorbidity Index  $\geq 4$ .

**Conclusions:** These data indicate that calcium, PTH, and kidney stones are important in predicting who are at greatest risk of HC. The Classification and Regression Tree can further help stratify risk for developing HC and allow surgeons to expedite parathyroidectomy accordingly.

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## Introduction

Hypercalcemic crisis (HC) is an uncommon, potentially fatal complication of primary hyperparathyroidism (PHPT) that

impacts numerous organ systems and requires acute hospitalization for management. Although some elevations in serum calcium can be well tolerated, symptoms of crisis are severe. Presentations of HC vary but may include nausea,

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\* Corresponding author. Department of Surgery, University of Wisconsin, 600 Highland Avenue, K4/739 CSC, Madison, WI 53792. Tel.: +1 608 263 1387; fax: +1 608 252 0912.

E-mail address: [randle@surgery.wisc.edu](mailto:randle@surgery.wisc.edu) (R.W. Randle).  
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vomiting, pancreatitis, profound weakness, cognitive disturbances, somnolence, acute kidney injury, and cardiac arrhythmias.<sup>1–3</sup> If treatment is delayed, HC can result in death.<sup>2</sup>

PHPT is the most common cause of hypercalcemia with or without crisis.<sup>2,4</sup> Treatment for HC begins with aggressive hydration and determination of the underlying cause. Parathyroidectomy provides the only cure for HC caused by PHPT. Removing the overactive gland or glands lowers the levels of parathyroid hormone (PTH) released into the blood thereby decreasing serum calcium.<sup>5,6</sup> In contrast to most parathyroid surgeries, which are largely elective, parathyroidectomy for HC is urgent and recommended during the same admission.

It remains unclear, however, which patients with PHPT are at greatest risk of developing HC. This knowledge would allow providers to expedite parathyroidectomy in patients with increased risk thereby avoiding hospitalization and complications associated with HC. Thus, the primary purpose of this study was to identify risk factors of HC in patients with PHPT. The secondary aim of this study was to characterize the presentation, operative outcomes, and pathology of patients with HC.

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## Methods

### Selection criteria

We performed a single-institution retrospective cohort study of patients who underwent parathyroidectomy from November 2000 to March 2016. Data were collected prospectively, and the University of Wisconsin Institutional Review Board approved the study. Some data were retrospectively gathered from the medical record including details on hospital admission, less common symptoms of hypercalcemia, and detailed medication lists. Patients included in the overall cohort had PHPT with a preoperative calcium level greater than or equal to 12 mg/dL. We used a minimum calcium level to limit our analysis to patients with a reasonably high risk of developing HC and to reduce the total number of cases available in the database to a manageable size.<sup>2</sup> We excluded patients if they had prior parathyroid surgery, a family history of related genetic syndromes, or age less than 18 y. Patients taking lithium were also excluded because lithium has been shown to increase serum calcium and PTH levels and likely reflects a different disease process.<sup>7</sup> Each patient was then classified into one of two groups, those with HC and those without HC.

### Definitions

We defined HC as requiring hospitalization for hypercalcemia before undergoing a parathyroidectomy. We gathered information on medications before admission (or surgery for those not admitted in HC) with a particular emphasis on those that impact serum calcium level. These medications included bisphosphonates, loop diuretics, thiazide diuretics, calcimimetics, vitamin D, multivitamins, calcium supplements, and hormonal therapies, such as estrogen.<sup>8</sup> Another variable we analyzed was the patients' Charlson Comorbidity Index (CCI), which provided an appraisal of patient comorbidities.<sup>9</sup>

## Surgery

We classified the types of parathyroidectomy that the patients underwent as a minimally invasive procedure, minimally invasive procedure—converted to open, or open four-gland exploration. Pathology was categorized as adenoma or hyperplasia, atypical adenoma, or cancer by a pathologist. We extracted these data from the pathology report. Our pathologists use the term “atypical adenoma” to describe adenomas with features of malignancies, such as banding fibrosis or mitotic activity, but lacking unequivocal evidence of invasive growth, as seen in carcinomas.<sup>10</sup>

## Statistical analysis

We performed a univariable analysis to compare patients with HC to those without HC by analyzing categorical variables with chi-square tests and continuous variables with Mann-Whitney *U* tests, due to lack of normality. We then performed forward stepwise multivariable logistic regression to identify predictors of hypercalcemic crisis. Patient age, gender, and all variables with  $P < 0.10$  in the univariable analysis served as candidate predictors for the multivariable analysis. We used a Classification and Regression Tree (CART) analysis to create a decision-making tool to classify patients into groups based on the risk of a patient in whom HC developed. CART combines recursive partitioning and regression methods to classify patients according to the outcome of interest.<sup>11</sup> The CART analysis algorithm goes through each value for the variable to determine the cutoff point that does the best job of differentiating patients with and without crisis. The cutoffs for each variable are computer generated, taking into account the relationships between the variables at the different levels (or branch points) of the classification tree. For this reason, some variables that are nonsignificant in logistic regression become significant at later branch points in the CART analysis (e.g., CCI). The decision tree model was 10-fold cross-validated. All analyses except the CART analysis were performed with SPSS 23 (IBM, Chicago, IL). The CART analysis was performed with R 3.3.1 “rpart” (Vienna, Austria).

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## Results

### Patient characteristics

From 11/2000 to 03/2016, there were 2344 initial parathyroidectomies performed for sporadic PHPT in adults. The final study cohort included 183 patients with a serum calcium greater than or equal to 12 mg/dL. There were 29 (15.8%) patients with HC and 154 (84.2%) patients without HC. Of HC patients with records available before admission, 72% (13/18) had health care encounters before experiencing HC where PHPT could potentially have been recognized and treated. Patients with and without HC were similar in age, gender, CCI, body mass index, and smoking status (Table 1). There were significant differences in several of the preoperative laboratory values between the two groups of patients. As expected, patients with HC had a higher median calcium level

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