Original Article

Opportunities to improve the diagnosis and treatment of primary hyperparathyroidism: retrospective cohort study

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Background: Although primary hyperparathyroidism (PHPT) is readily diagnosed biochemically and can be cured with low-risk surgery, it is often underrecognized and undertreated. Our objectives were to characterize, within our health system, how often patients with hypercalcemia were evaluated for PHPT and how often patients with PHPT underwent definitive treatment with parathyroidectomy.

Methods: Ambulatory patients aged 18 years or older seen at our health system between January 2018 and June 2023 with chronic hypercalcemia were identified from the medical record. After excluding causes of secondary hyperparathyroidism, the proportion of patients with parathyroid hormone (PTH) tests was calculated. Among patients with biochemical evidence of PHPT, the proportion of patients who underwent parathyroidectomy was calculated. Multivariable logistic regression was used to identify factors associated with an evaluation for PHPT and, separately, with parathyroidectomy.

Results: Of 7,675 patients with chronic hypercalcemia, 3,323 (43.3%) had a PTH test obtained within 6 months. An age between 40–49 *vs.* <30 years [(odds ratio (OR) =3.2; 95% confidence interval (CI): 1.8–5.6; P<0.001], a serum calcium level between 11.6–12.0 *vs.* <11.0 mg/dL (OR =3.9; 95% CI: 3.2–4.7; P<0.001), and osteoporosis (OR =3.1; 95% CI: 2.7–3.5; P<0.001) were associated with an evaluation for PHPT. Among those with PTH levels, 1,327 (39.9%) had PHPT but only 916 (69.0%) were recognized. Three hundred and forty-five (26.0%) patients with PHPT underwent parathyroidectomy. An increasing number of surgical indications was associated with parathyroidectomy (P<0.001), though overall rates remained less than 40%. Among indications for surgery, including age and serum total calcium level, only osteoporosis was associated with parathyroidectomy (OR =2.0; 95% CI: 1.4–2.8; P<0.001).

Conclusions: In this study, more than half of patients with chronic hypercalcemia were not evaluated for PHPT. Among patients with biochemical evidence of PHPT, one-third were unrecognized and only one-in-four received curative treatment. Opportunities to improve the management of PHPT exist within our large integrated health system.

Keywords: Surgery; hypercalcemia; parathyroidectomy; hyperparathyroidism; underdiagnosis

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Introduction

Primary hyperparathyroidism (PHPT) is a chronic condition caused by the autonomous overproduction of parathyroid hormone (PTH) from one or more parathyroid glands. It is one of the most common causes of hypercalcemia in the outpatient setting, particularly in primary care (1). Left untreated, PHPT can cause premature osteoporosis, fragility fractures, recurrent kidney stones, impaired renal function, and other harmful sequelae including increased risk for cardiovascular disease and death (2-4). Surgery to remove the culprit gland(s) is the only current definitive treatment (5).

Every year, more than 100,000 patients in the U.S. are diagnosed with PHPT, yet this is an underestimate as there are well-known opportunities to improve the diagnostic process that have been recognized for more than a decade (6). After hypercalcemia is identified, the next step is to determine whether it is caused by PHPT. However, this step—obtaining a PTH level once hypercalcemia is identified—is frequently overlooked (7). These errors of omission can delay diagnosis and treatment, likely contributing to the estimated 5% of U.S. adult outpatients who experience diagnostic errors annually (8).

Moreover, when PHPT is recognized and diagnosed, definitive treatment with parathyroidectomy is underutilized, including among patients who meet guideline-concordant indications for surgery (9,10). Parathyroid surgery is generally low risk, can be performed on an outpatient basis in selected patients, and cures more than 95% of patients (5). Weighing the potential benefits and low risks of surgery, patients may be excluded from curative treatment if surgery is neither considered nor offered (11).

Mass General Brigham (MGB) is an integrated healthcare system in Massachusetts comprised of two academic medical centers, seven community hospitals, three specialty hospitals, and a large network of community-based physician office practices with more than 1,300 primary care providers. We sought to understand, within our health system, how often patients with hypercalcemia were evaluated for PHPT and how often patients with PHPT underwent definitive treatment with parathyroidectomy. We hypothesized that the rates of both would be higher than historical studies over the past 10 years, which may have brought increased awareness of the underdiagnosis and undertreatment of PHPT. Any low rates, if present, could potentially serve as quality improvement opportunities within our health system. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-128/rc).

Highlight box

Key findings

- In this retrospective cohort study conducted at a large integrated health system in the U.S., primary hyperparathyroidism (PHPT) remains underdiagnosed and undertreated.

What is known and what is new?

- PHPT is a common endocrine disorder with negative sequelae. Surgery is the only current cure for PHPT. For more than 10 years, studies have reported that PHPT is underdiagnosed and undertreated, even among patients who meet international consensus guidelines for surgical treatment.
- This study, conducted in a modern cohort of patients, demonstrates that PHPT remains underdiagnosed and undertreated. Little progress has been made for this common chronic condition.

What is the implication, and what should change now?

- Beyond continued education and advances in perioperative management and surgical technique, innovative efforts to improve PHPT management are urgently needed.

Methods

Data source and study cohort

For this retrospective cohort study, patients aged 18 years or older in the outpatient setting between January 1, 2018 and June 30, 2023 with at least one available serum total calcium laboratory test result were identified from the MGB Research Patient Data Registry (RPDR), a centralized clinical data warehouse that gathers information from several system-wide and external data sources, including the electronic health record, on all patients seen at MGB (12). We obtained data on patient demographics, diagnoses using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) coding system, laboratory tests using Logical Observation Identifiers Names and Codes (LOINC) codes, procedures, and clinic encounters. Data, including information that could identify individual participants, were accessed on July 14, 2023 for this research. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As a retrospective review of pre-existing medical record data, the MGB IRB determined the study to be exempt from oversight (protocol No. 2022P002634) and

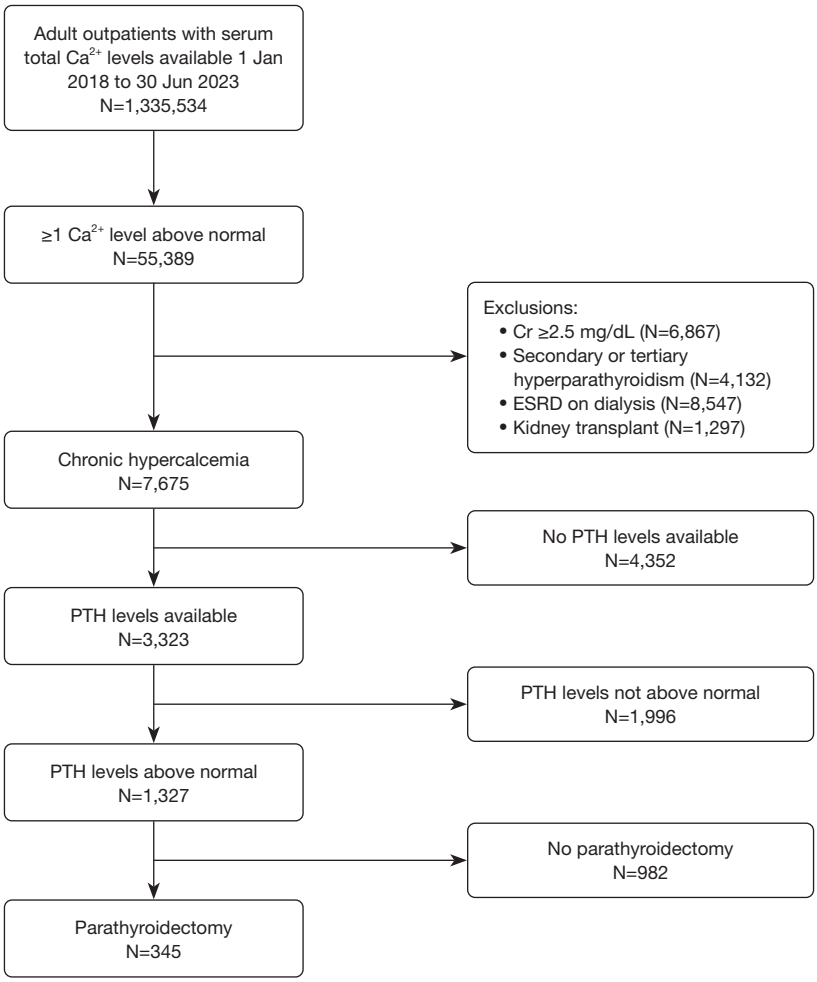

Figure 1 Cohort creation for study. Note that the reasons for exclusion were not mutually exclusive. Chronic hypercalcemia is defined as two serum total calcium levels above the reference range for normal within 6 months. Cr, creatinine; ESRD, end-stage renal disease; PTH, parathyroid hormone.

waived the requirement for informed consent.

To form the analytic cohort (*Figure 1*), we identified patients with at least one serum total calcium level above the reference range for normal and excluded those with serum creatinine ≥2.5 mg/dL. Patients diagnosed with secondary or tertiary hyperparathyroidism, who were dialysis dependent, or with a kidney transplant were also excluded based on ICD-10 diagnosis codes (13). Specifically, laboratory values were not used to identify and exclude patients with secondary or tertiary hyperparathyroidism. The reference range for calcium levels rather than an absolute level was used to account for varying reference ranges by laboratory. Patients with chronic hypercalcemia, defined as two serum total calcium levels above the reference range for normal within 6 months, were then identified (14,15). Two separate levels were more likely to represent true chronic hypercalcemia rather than spurious laboratory test results.

Diagnostic evaluation

We categorized patients into those with and without available serum intact PTH laboratory test results within 6 months of chronic hypercalcemia. Patients with PTH levels above the reference range for normal were considered to have PHPT (i.e., classic or hypercalcemic PHPT). To ensure high diagnostic specificity relying on biochemical criteria, we did not examine patients for normohormonal

PHPT. We further categorized patients with PHPT into those with and without documented diagnosis codes for hyperparathyroidism (ICD-10 E21.0, E21.2, E21.3, E21.4, E21.5, D35.1, D44.2), reflecting patients with recognized and unrecognized PHPT, respectively.

Definitive treatment

Patients who were evaluated by an endocrinologist or surgeon from General Surgery, Surgical Oncology or Otorhinolaryngology disciplines after meeting our definition for PHPT were identified from encounter data. Patients who underwent parathyroidectomy were identified using Common Procedural Terminology® codes (60500, 60502, 60505).

Indications for surgery followed the Guidelines from the Fifth International Workshop and were documented prior to parathyroidectomy (10). Patients with nephrolithiasis, osteoporosis, or pathologic bone fractures were identified using ICD-10 codes (9,15,16). Patients with serum total calcium level >1 mg/dL above the reference range for normal, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, or hypercalciuria (>250 mg/day in women; >300 mg/day in men) were identified using laboratory test results, when available.

Patient characteristics

Additional patient details included age, sex, race (Black, White, other, unknown/declined), Hispanic ethnicity, insurance status (commercial, Medicare, Medicaid, other, unknown/declined), comorbidity burden using the Charlson comorbidity index (CCI) (17), and 25-OH vitamin D levels.

Statistical analysis

Descriptive analyses were performed using Student's *t*-test, Wilcoxon rank-sum test, χ^2 test for association, or Fisher's exact test, where appropriate. We tested the associations of the number of surgical indications with rates of surgical evaluation and parathyroidectomy, separately, using the Cochran-Armitage test for trend.

Among patients with chronic hypercalcemia, multiple logistic regression was used to identify factors associated with the presence of PTH test results within six months. Among patients with PHPT, a separate multiple logistic regression model identified factors associated with parathyroidectomy. Factors with P values <0.2 on univariate analyses were included in the respective multivariable models. Factors with missingness (e.g., 24-hour urine calcium) were excluded from the models. However, as sensitivity analyses, we conducted complete case analyses with all available variables meeting the P value <0.2 threshold.

Tests of significance were two-sided with alpha set at 0.05. SAS v9.4 (SAS Institute; Cary, NC, USA) was used.

Results

Patient cohort

Of 1,335,534 adult outpatients with at least one serum total calcium test result available, 55,398 (4.1%) had at least one level above normal (*Figure 1*). After excluding patients with serum creatinine ≥2.5 mg/dL (n=6,867), diagnosed with secondary or tertiary hyperparathyroidism (n=4,132), who were dialysis dependent (n=8,547), or with a kidney transplant (n=1,297), we identified 7,675 (18.9%) patients with chronic hypercalcemia from the remaining 40,573 patients. Patients with chronic hypercalcemia were predominantly non-Hispanic (n=6,559; 85.5%), White (n=6,337; 82.6%), females (n=4,868; 63.4%) with mean [standard deviation (SD)] age 66.2 (16.1) years and median [interquartile range (IQR)] calcium level 11.0 (10.8–11.5) mg/dL (*Table 1*). Most were covered by Medicare (n=3,779; 49.2%).

Diagnostic evaluation

Of 7,675 patients with chronic hypercalcemia, 3,323 (43.3%) had PTH tests obtained within 6 months and 4,352 (56.7%) did not. Patients with available PTH tests, compared to those without, were on average 1.6 years older (P<0.001) and more often female (68.4% *vs.* 59.6%, P<0.001) with Medicare coverage (51.1% *vs.* 47.8%, P<0.001) (*Table 1*).

We examined seven indications for surgery as shown in *Table 1*: age <50 years, kidney stones, osteoporosis, pathologic bone fracture, serum total calcium >1 mg/dL above normal, eGFR <60 mL/min/1.73 m^2 and hypercalciuria. Patients with PTH tests, compared to without, were less often younger than 50 years of age (10.4% *vs.* 15.9%, P<0.001) and more often had kidney stones (11.0% *vs.* 7.9%, P<0.001). Patients with PTH tests also more often had osteoporosis (41.4% *vs.* 20.8%, P<0.001), pathologic bone

Table 1 Patients with chronic hypercalcemia who had PTH levels and patients with PHPT who underwent parathyroidectomy

Patient characteristics	Total	PTH levels			Parathyroidectomy		
		Not available	Available	P value	No	Yes	P value
Number, n (%)	7,675 (100.0)	4,352 (56.7)	3,323 (43.3)		982 (74.0)	345 (26.0)	
Age (years), mean (SD)	66.2 (16.1)	65.5 (17.4)	67.1 (14.1)	<0.001	69.8 (13.6)	61.0 (13.6)	<0.001
Age, n (%)				<0.001			<0.001
<30 years	307 (4.0)	244 (5.6)	63 (1.9)		8 (0.8)	8 (2.3)	
30–39 years	287 (3.7)	198 (4.6)	89 (2.7)		22 (2.2)	18 (5.2)	
40–49 years	445 (5.8)	251 (5.8)	194 (5.8)		47 (4.8)	38 (11.0)	
50–59 years	1,110 (14.5)	583 (13.4)	527 (15.9)		130 (13.2)	84 (24.4)	
60–69 years	1,890 (24.6)	1,053 (24.2)	837 (25.2)		231 (23.5)	87 (25.2)	
70–79 years	2,129 (27.7)	1,116 (25.6)	1,013 (30.5)		299 (30.5)	91 (26.4)	
≥80 years	1,507 (19.6)	907 (20.8)	600 (18.1)		245 (25.0)	19 (5.5)	
Female, n (%)	4,868 (63.4)	2,594 (59.6)	2,274 (68.4)	<0.001	731 (74.4)	268 (77.7)	0.02
Race, n (%)				0.67			0.004
Black	622 (8.1)	353 (8.1)	269 (8.1)		115 (11.7)	25 (7.3)	
White	6,337 (82.6)	3,598 (82.7)	2,739 (82.4)		758 (77.2)	296 (85.8)	
Other	495 (6.5)	270 (6.2)	225 (6.8)		73 (7.4)	20 (5.8)	
Unknown/declined	221 (2.9)	131 (3.0)	90 (2.7)		36 (3.7)	4 (1.2)	
Hispanic ethnicity, n (%)	258 (3.4)	136 (3.1)	122 (3.7)	0.30	47 (4.8)	11 (3.2)	0.30
Unknown/declined	858 (11.2)	499 (11.5)	359 (10.8)		119 (12.1)	36 (10.4)	
Insurance status, n (%)				<0.001			<0.001
Medicare	3,779 (49.2)	2,081 (47.8)	1,698 (51.1)		554 (56.4)	142 (41.2)	
Medicaid	918 (12.0)	569 (13.1)	349 (10.5)		98 (10.0)	21 (6.1)	
Commercial	2055 (26.8)	1,146 (26.3)	909 (27.4)		224 (22.8)	151 (43.8)	
Other	861 (11.2)	508 (11.7)	353 (10.6)		100 (10.2)	31 (9.0)	
Uninsured/unknown	62 (0.8)	48 (1.1)	14 (0.4)		6 (0.6)	0 (0.0)	
Charlson comorbidity index, n (%)				0.84			<0.001
0	2,868 (37.4)	1,625 (37.3)	1,243 (37.4)		335 (34.1)	166 (48.1)	
1	1,707 (22.2)	978 (22.5)	729 (21.9)		190 (19.4)	90 (26.1)	
2+	3,100 (40.4)	1,749 (40.2)	1,351 (40.7)		457 (46.5)	89 (25.8)	
Laboratory values, median (IQR)							
Serum total calcium (mg/dL)	11.0 (10.8–11.5)	10.9 (10.7–11.3)	11.2 (10.9–11.7)	<0.001	11.2 (10.9–11.6)	11.3 (11.0–11.7)	<0.001
Serum intact PTH (pg/mL)	58.0 (28.0–97.0)	–	58.0 (28.0–97.0)	–	105.0 (86.0–139.0)	119.0 (93.0–154.0)	<0.001
Serum creatinine (mg/dL)	1.2 (0.9–1.5)	1.2 (1.0–1.5)	1.1 (0.9–1.5)	0.004	1.2 (0.9–1.5)	1.0 (0.9–1.2)	<0.001
25-OH vitamin D (ng/mL) (n=4,544)	40.0 (29.0–53.0)	38.0 (27.0–50.0)	41.0 (30.0–54.0)	<0.001	39.0 (29.0–51.0)	43.0 (33.5–55.0)	<0.001
Surgical indications, n (%)							
Age <50 years	1,039 (13.5)	693 (15.9)	346 (10.4)	<0.001	77 (7.8)	64 (18.6)	<0.001
Kidney stones	706 (9.2)	342 (7.9)	364 (11.0)	<0.001	119 (12.1)	61 (17.7)	0.009
Osteoporosis	2,281 (29.7)	907 (20.8)	1,374 (41.4)	<0.001	474 (48.3)	210 (60.9)	<0.001
Pathologic bone fracture	421 (5.5)	192 (4.4)	229 (6.9)	<0.001	82 (8.4)	6 (1.7)	<0.001
Serum total calcium >1 mg/dL above normal	2,100 (27.4)	876 (20.1)	1,224 (36.8)	<0.001	337 (34.3)	153 (44.4)	0.001
eGFR <60 mL/min/1.73 m^2 (n=7,661)	4,342 (56.7)	2,441/4,340 (56.2)	1,901/3,321 (57.2)	0.38	612 (62.3)	139 (40.3)	<0.001
Elevated 24-hour urine calcium (n=520)	165 (31.7)	2/6 (33.3)	163/514 (31.7)	>0.99	47/230 (20.4)	79/146 (54.1)	<0.001
>250 mg/24 hour for women (n=404)	128 (31.7)	2/5 (40.0)	126/399 (31.6)	0.65	38/182 (20.9)	60/113 (53.1)	<0.001
>300 mg/24 hour for men (n=116)	37 (31.9)	0/1 (0.0)	37/115 (32.2)	–	9/48 (18.8)	19/33 (57.6)	<0.001

PTH, parathyroid hormone; PHPT, primary hyperparathyroidism; SD, standard deviation; IQR, interquartile range; eGFR, estimated glomerular filtration rate.

Table 2 Factors associated with available PTH levels within 6 months of chronic hypercalcemia (n=7,675)

Covariate	Odds ratio (95% CI)	P value
Age		<0.001
<30 years	Reference	
30–39 years	2.4 (1.3–4.4)	0.006
40–49 years	3.2 (1.8–5.6)	<0.001
50–59 years	2.8 (1.6–4.7)	<0.001
60–69 years	2.0 (1.2–3.5)	0.009
70–79 years	2.0 (1.2–3.5)	0.01
≥80 years	1.9 (1.1–3.3)	0.02
Sex		<0.001
Male	Reference	
Female	1.4 (1.2–1.6)	<0.001
Insurance status		0.02
Commercial	Reference	
Medicare	0.86 (0.73–1.0)	0.09
Medicaid	0.69 (0.55–0.88)	0.002
Other/uninsured/unknown	0.85 (0.68–1.1)	0.17
Laboratory values		
Calcium		<0.001
<11.0 mg/dL	Reference	
11.1–11.5 mg/dL	2.8 (2.5–3.3)	<0.001
11.6–12.0 mg/dL	3.9 (3.2–4.7)	<0.001
>12.0 mg/dL	1.7 (1.3–2.1)	<0.001
Creatinine	0.84 (0.71–0.99)	0.04
Indications for surgery		
Kidney stones	1.8 (1.5–2.1)	<0.001
Osteoporosis	3.1 (2.7–3.5)	<0.001
Bone fracture	0.85 (0.66–1.1)	0.23

PTH, parathyroid hormone; CI, confidence interval.

Table 3 Factors associated with available PTH levels within 6 months of chronic hypercalcemia using a complete case analysis (n=4,544)

Covariate	Odds ratio (95% CI)	P value
Age		0.003
<30 years	Reference	
30–39 years	2.4 (1.2–4.6)	0.01
40–49 years	2.5 (1.4–4.7)	0.003
50–59 years	2.4 (1.3–4.2)	0.003
60–69 years	1.7 (0.94–2.9)	0.08
70–79 years	1.8 (1.003–3.1)	0.049
≥80 years	1.7 (0.96–3.1)	0.07
Sex		<0.001
Male	Reference	
Female	1.4 (1.2–1.6)	<0.001
Insurance status		0.005
Private	Reference	
Medicare	0.84 (0.70–1.02)	0.07
Medicaid	0.62 (0.5–0.8)	<0.001
Other/uninsured/unknown	0.86 (0.7–1.1)	0.22
Laboratory values		
Calcium		<0.001
<11.0 mg/dL	Reference	
11.1–11.5 mg/dL	2.8 (2.4–3.3)	<0.001
11.6–12.0 mg/dL	3.7 (3.0–4.6)	<0.001
>12.0 mg/dL	1.4 (1.1–1.7)	0.008
Creatinine	0.84 (0.70–1.01)	0.07
25-OH vitamin D	0.995 (0.992–0.999)	0.01
Indications for surgery		
Kidney stones	1.6 (1.3–1.9)	<0.001
Osteoporosis	2.2 (1.9–2.5)	<0.001
Bone fracture	0.72 (0.55–0.94)	0.02

PTH, parathyroid hormone; CI, confidence interval.

fractures (6.9% *vs.* 4.4%, P<0.001), and serum total calcium levels >1 mg/dL above normal (36.8% *vs.* 20.1%, P<0.001) as compared to those without PTH tests.

On multivariable analysis, patients were more likely to have PTH tests if they were between 40–49 years of age *vs.* <30 years [odds ratio (OR) =3.2; 95% confidence interval (CI): 1.8–5.6; P<0.001], if they had a serum calcium level between 11.6–12.0 *vs.* <11.0 mg/dL (OR =3.9; 95% CI: 3.2–4.7; P<0.001), and if they had osteoporosis (OR =3.1; 95% CI: 2.7–3.5; P<0.001) (*Table 2*). Patients with Medicaid coverage had decreased odds of having PTH tests compared to those with commercial insurance (OR =0.69; 95% CI: 0.55–0.88; P=0.002). Using only complete cases (n=4,544), patterns remained similar except that older patient groups and patients with bone fractures had lower odds of having PTH tests (OR =0.72; 95% CI: 0.55–0.94; P=0.02) (*Table 3*).

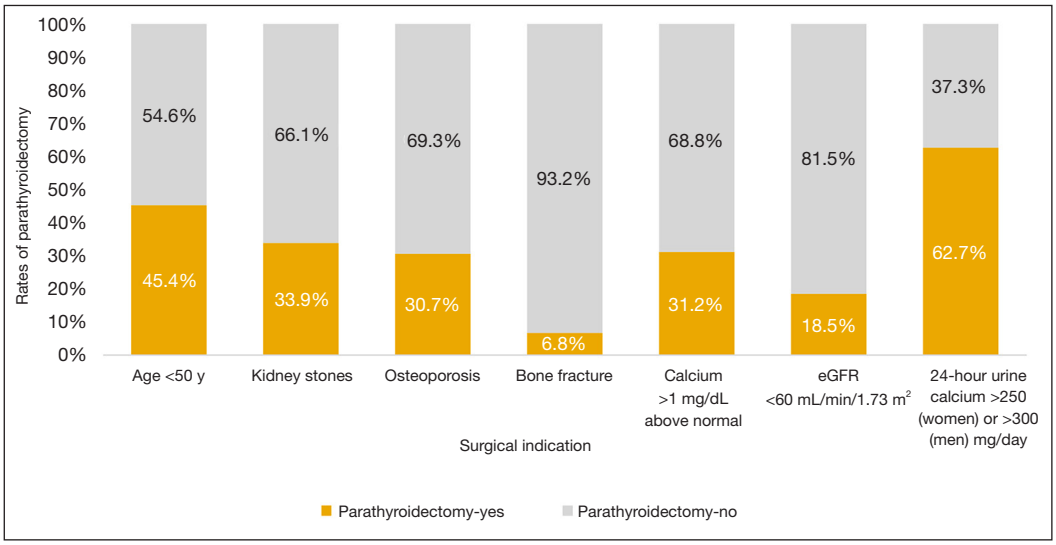

Figure 2 Rates of parathyroidectomy by surgical indication. eGFR, estimated glomerular filtration rate.

Of 3,323 patients with chronic hypercalcemia and available PTH test results, 1,327 (39.9%) had PTH levels above normal, consistent with PHPT. Of these, 916 (69.0%) had a documented diagnosis code for hyperparathyroidism and 411 (31.0%) did not.

Definitive treatment

Of 1,327 patients with PHPT, 525 (39.6%) were evaluated by an endocrinologist, 374 (28.2%) were evaluated by a surgeon, and 345 (26.0%) underwent parathyroidectomy. Counts are not mutually exclusive among these three categories. The median (IQR) number of months to an endocrinology evaluation was 3.6 (1.2–12.4) months and to a surgical evaluation 6.3 (1.7–19.7) months. An increasing number of surgical indications was correlated with surgical evaluations (P<0.001).

The median (IQR) number of months to parathyroidectomy was 8.2 (3.8–19.7) months. Patients who underwent parathyroidectomy, compared to those who did not, were on average 8.8 years younger (P<0.001) and more often had no comorbidities (CCI: 0; 48.1% *vs.* 34.1%, P<0.001). They were also more often White (85.8% *vs.* 77.2%, P=0.004) with commercial insurance (43.8% *vs.* 22.8%, P<0.001).

Of the 1,327 patients in our cohort with biochemical evidence of PHPT, 1,231 (92.8%) had at least one surgical indication. The proportion of patients who underwent parathyroidectomy by surgical indication varied (*Figure 2*). Patients with hypercalciuria underwent parathyroidectomy 62.7% of the time, whereas patients with pathologic bone fractures underwent parathyroidectomy 6.8% of the time. An increasing number of surgical indications was significantly associated with parathyroidectomy (P<0.001, *Figure 3*).

On multivariable analysis, patients who were 80 years or older had the lowest odds of parathyroidectomy (OR =0.12; 95% CI: 0.03–0.44; P=0.002), whereas comorbidity burden based on the CCI was not associated with parathyroidectomy (*Table 4*). Patients who were Black *vs.* White (OR =0.46; 95% CI: 0.26–0.81; P=0.008) or had Medicare (OR =0.54; 95% CI: 0.35–0.82; P=0.004) or Medicaid (OR =0.49; 95% CI: 0.26–0.92; P=0.03) coverage *vs.* commercial insurance also had lower odds of parathyroidectomy. Among indications for surgery, including age and serum calcium level, only osteoporosis was associated with parathyroidectomy (OR =2.0; 95% CI: 1.4–2.8; P<0.001). Consultations with an endocrinologist (OR =1.6; 95% CI: 1.1–2.2; P=0.01) or surgeon (OR =9.1; 95% CI: 6.6–12.6; P<0.001) were strongly associated with parathyroidectomy. Using complete cases (n=373), patterns remained robust though were no longer statistically significant likely due to the decreased sample size (*Table 5*). Interestingly, hypercalciuria was strongly associated with parathyroidectomy (OR =3.9; 95% CI: 2.1–7.4; P<0.001), but not the presence or history of kidney stones (OR =1.3; 95% CI: 0.59–2.9).

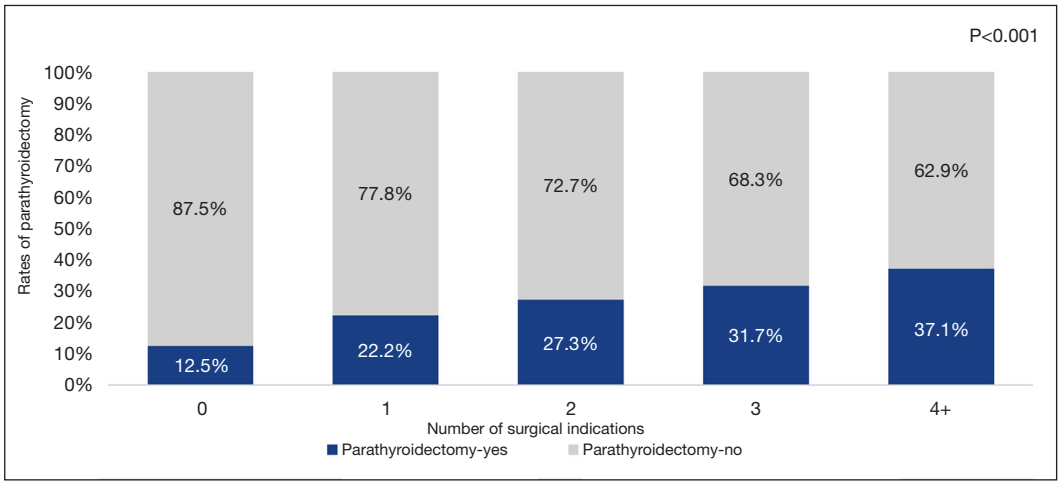

Figure 3 Rates of parathyroidectomy by number of surgical indications.

Discussion

In this study, more than 50% of patients with chronic hypercalcemia were not evaluated for PHPT. Younger age, osteoporosis, and higher serum calcium levels were associated with an evaluation for PHPT. Among patients with biochemical evidence of PHPT, 31% were unrecognized and 26% underwent parathyroidectomy. Though patients with more surgical indications more frequently underwent surgical evaluation and parathyroidectomy, as expected, overall rates remained low. Consultations with an endocrinologist or surgeon were associated with parathyroidectomy. Taken together, progress has not been made over the last 10 years to improve the diagnosis and treatment. These data suggest that efforts are needed to improve the diagnostic evaluation and treatment of PHPT within our large integrated health system, and more broadly.

Our findings are consistent with previous studies highlighting opportunities to improve the detection and management of PHPT. Studies from the Southern U.S. reported 70–85% of patients with hypercalcemia did not have accompanying PTH levels, 25% of patients with biochemical evidence of PHPT were unrecognized, and 20% were referred for surgical evaluation (16,18,19). Similarly in studies conducted in the Western U.S., approximately 50% of patients with hypercalcemia did not have PTH levels and 20–30% with PHPT underwent parathyroidectomy (9,14,20,21). In the Midwest U.S. (22,23), one large academic medical center reported two-thirds of hypercalcemic patients were not further evaluated with PTH levels and less than 20% with PHPT underwent parathyroidectomy (23). Our study, conducted in Northeastern US, completes the geographic landscape with similar findings. National studies also found similar, if not worse, results (13,24-27). Importantly, this phenomenon is not unique to the US. Studies in Sweden (28) and the UK (29,30) have reported similar trends. For example, Sillars *et al.* (30) reported that approximately half of patients with chronic hypercalcemia were evaluated with PTH levels. Solutions are now needed.

As previously discussed, complications from PHPT are systemic, chronic, and can be costly. A recent large retrospective cohort analysis of over 100,000 women over the age of 50 estimates a mean annual healthcare cost of between $44,311 and $71,561 among patients with a fragility fracture and an estimated U.S. healthcare systems cost of $25 billion by 2025 (31). Furthermore, fragility hip fractures in the elderly contribute to significant long-term disability, decreased quality of life, reduced life expectancy by on average 2.7%, and are associated with a 1-year mortality of 10–66% (32,33). Regarding genitourinary complications, in 2014, the economic burden of nephrolithiasis exceeded $4.5 billion (>$9 billion in 2024 USDs) (34). Meanwhile, the annual cost of surgically managed PHPT in the U.S. is estimated at $282 million in 1998 (35). Unfortunately, the most recent "break-even" analysis suggesting the cost of definitive diagnosis and surgical management of PHPT matches the cost of ongoing medical management of possible complications at 5.5 years was conducted in the late 1970s, also only at a single tertiary center (36). While

Table 4 Factors associated with parathyroidectomy among those with PHPT (n=1,327)

Covariate	Odds ratio (95% CI)	P value
Age		0.001
<30 years	Reference	
30–39 years	1.1 (0.28–4.4)	0.88
40–49 years	0.65 (0.18–2.3)	0.51
50–59 years	0.45 (0.14–1.5)	0.19
60–69 years	0.33 (0.01–1.1)	0.07
70–79 years	0.37 (0.10–1.3)	0.12
≥80 years	0.12 (0.03–0.44)	0.002
Race		0.004
White	Reference	
Black	0.46 (0.26–0.81)	0.008
Other	0.48 (0.24–0.93)	0.03
Unknown/declined	0.29 (0.08–1.0)	0.05
Insurance status		0.009
Commercial	Reference	
Medicare	0.54 (0.35–0.82)	0.004
Medicaid	0.49 (0.26–0.92)	0.03
Other/uninsured/unknown	0.56 (0.31–1.0)	0.051
Charlson comorbidity index		0.57
0	Reference	
1	1.2 (0.80–1.8)	0.40
2+	0.94 (0.61–1.5)	0.78
Laboratory values		
Calcium		0.15
<11.0 mg/dL	Reference	
11.1–11.5 mg/dL	0.94 (0.64–1.4)	0.76
11.6–12.0 mg/dL	1.6 (0.97–2.5)	0.07
>12.0 mg/dL	0.94 (0.51–1.7)	0.84
PTH	1.005 (1.003–1.007)	<0.001
Creatinine	0.31 (0.16–0.60)	<0.001
Indications for surgery		
Kidney stones	1.5 (0.95–2.3)	0.09
Osteoporosis	2.0 (1.4–2.8)	<0.001
Bone fracture	0.24 (0.09–0.6)	0.005
eGFR <60 mL/min/1.73 m^2	1.2 (0.8–1.9)	0.43
Endocrinology evaluation	1.6 (1.1–2.2)	0.01
Surgical evaluation	9.1 (6.6–12.6)	<0.001

PHPT, primary hyperparathyroidism; CI, confidence interval; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate.

Table 5 Factors associated with parathyroidectomy among those with PHPT using a complete case analysis (n=373)

Covariate	Odds ratio (95% CI)	P value
Age		0.55
<30 years	Reference	
30–39 years	0.31 (0.03–3.6)	0.35
40–49 years	0.11 (0.01–0.99)	0.048
50–59 years	0.20 (0.03–1.5)	0.12
60–69 years	0.14 (0.02–1.1)	0.06
70–79 years	0.17 (0.02–1.4)	0.11
≥80 years	0.15 (0.02–1.3)	0.09
Race		0.06
White	Reference	
Black	0.38 (0.15–0.99)	0.049
Other	1.5 (0.45–4.8)	0.52
Unknown/declined	0.20 (0.03–1.2)	0.08
Insurance status		0.66
Private	Reference	
Medicare	0.67 (0.32–1.4)	0.29
Medicaid	0.69 (0.24–2.0)	0.50
Other/uninsured/unknown	0.65 (0.25–1.7)	0.37
Charlson comorbidity index		0.13
0	Reference	
1	1.3 (0.65–2.6)	0.46
2+	0.56 (0.26–1.2)	0.15
Laboratory values		
Calcium		0.13
<11.0 mg/dL	Reference	
11.1–11.5 mg/dL	0.70 (0.37–1.3)	0.28
11.6–12.0 mg/dL	1.8 (0.74–4.3)	0.20
>12.0 mg/dL	0.69 (0.12–2.4)	0.57
PTH	1.01 (0.999–1.01)	0.08
Creatinine	1.15 (0.36–3.7)	0.81
25-OH vitamin D	1.02 (1.01–1.04)	0.008
Indications for surgery		
Kidney stones	1.3 (0.59–2.9)	0.50
Osteoporosis	1.6 (0.84–3.1)	0.15
Bone fracture	0.25 (0.06–1.1)	0.058
eGFR <60 mL/min/1.73 m^2	1.3 (0.57–2.7)	0.58
24-hour urine calcium >250 (women)/>300 (men) mg/24 hours	3.9 (2.1–7.4)	<0.001
Endocrinology evaluation	0.69 (0.38–1.3)	0.23
Surgical evaluation	8.1 (4.5–14.6)	<0.001

PHPT, primary hyperparathyroidism; CI, confidence interval; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate.

some of the aforementioned studies do not specifically address PHPT and its sequelae, it can be hypothesized that the economic burden of untreated PHPT is similar and a reasonable extrapolation. However, more modern economic evaluation studies focusing specifically on PHPT are needed, keeping in mind the patient's perspective.

The diagnostic process requires collaboration among health care professionals, patients, and their families (8). Recognizing this, Behnke *et al.* (37) attempted to improve PHPT diagnosis and treatment by directly informing patients. They identified from the medical record and sent letters to 396 patients with hypercalcemia, asking them to discuss with their primary care providers whether obtaining a PTH test would be appropriate. After 6 months, 20 (5%) patients had a new PTH test, of which half were found to have elevated levels, resulting in referrals for surgical or endocrinological evaluation. With immediate access to their medical records and laboratory test results, activated patients may certainly bring abnormal results to the attention of their providers. However, a multimodal approach is likely needed.

Automated electronic feedback based upon abnormal test results may be an approach to improve PHPT diagnosis. Leveraging health information technology, Dawood *et al.* (15) built electronic clinical decision support (CDS) within the electronic health record to prompt providers to obtain PTH levels in patients with hypercalcemia. They observed not only a 6-fold increase in serum PTH laboratory test results among outpatients with chronic hypercalcemia, but also increases in appropriate downstream diagnostic and therapeutic interventions without further prompting. Soon, electronic CDS tools that leverage artificial intelligence will likely play a greater role to help identify patients at risk and nudge clinicians to perform the next best steps, while also considering contemporary management guidelines and potentially patient-reported preferences (38). These innovations must, nevertheless, be balanced with the real concerns of alert fatigue and overdiagnosis (39).

Relying on structured medical record data, we could not identify the rationales for patient management. Understanding why insufficient PHPT management from detection to diagnosis to treatment is needed to affect change. Asban *et al.* (40) and Dombrowsky *et al.* (41) attempted to understand causes by reviewing detailed clinician notes and found that the primary documented reason for underutilization of surgery was because a non-surgeon informed them that surgery offered no benefit. Hypercalcemia was frequently attributed to a high calcium diet, vitamin D use, or thiazide diuretic use. High-quality qualitative research is needed to better understand why patients are underdiagnosed and undertreated for PHPT so that behavioral interventions can be designed and implemented.

While the underdiagnosis and undertreatment of PHPT is pervasive today, efforts to improve diagnosis should balance the risks of overdiagnosis and overtreatment (8,42). With increased use of "routine" laboratory tests, more subtle cases of PHPT may be detected that could be considered preclinical disease. For example, normocalcemic PHPT may represent an early form of classic PHPT, but the natural history of these cases is unclear. Nevertheless, as Lorenz *et al.* (25) reported, delays in diagnosis and treatment of even mild PHPT are associated with increased complications over a relatively short period. Early detection and intervention may therefore prevent disease progression in some patients. Until clearer evidence becomes available, treatment should be personalized based on factors like symptom burden, management guidelines, surgical risk, and patient preferences.

This study has other limitations. First, as a retrospective study involving one health system with a restricted time horizon, results may not be representative and therefore biased to the available data. It is plausible that patients were evaluated for PHPT prior to the start of the study period, thus serving to underestimate our results. Our study period overlapped with that of the coronavirus disease 2019 (COVID-19) pandemic, which may have also underestimated our results. Second, we chose to maximize the specificity of PHPT diagnosis and considered only classic PHPT. Though other subtle biochemical profiles, such as normocalcemic or normohormonal PHPT, were discounted, we still observed low rates of PHPT evaluation and treatment based on the most overt and clearcut definition of PHPT. Including more subtle manifestations of PHPT would only serve to magnify our results. Further, when identifying quality improvement targets and allocating resources, more overt cases should be recognized and treated before moving to these other subtler PHPT variants. These subtler forms often require specialist expertise to diagnose, and thus clinical algorithms alone may not be sufficient or appropriate. Third, along the same logic, we intentionally did not consider albumin correction nor serum ionized calcium concentration because our goal was to identify straightforward scenarios whereby evaluation of hypercalcemia should occur in busy, routine clinical

practice. Patients with hypoalbuminemia would also serve to magnify our results. We attempted to minimize situations of pseudohypercalcemia due to hyperalbuminemia by requiring two persistently elevated total serum calcium levels over 6 months following others (13,15,20). Ostensibly, the astute clinician who considers obtaining a serum ionized calcium concentration would likely order an accompanying PTH level but testing this hypothesis was not the aim of the present study. Fourth, we did not consider whether patients were taking biotin, which can lead to falsely low PTH levels. While this may decrease the proportion of patients with PHPT in this study, the consideration of biotin does not alter the appropriate evaluation of hypercalcemia by obtaining a PTH test. Last, ICD-10 diagnosis codes were used to identify PHPT sequelae. Future studies could consider other more sensitive approaches leveraging unstructured medical record data, such as natural language processing and other artificial intelligence methods, to sift through imaging report narratives or the images themselves. Our estimates are thus conservative due to these limitations.

Conclusions

In conclusion, our analysis revealed gaps and missed opportunities in the detection, diagnosis, and treatment of PHPT within our health system despite the study limitations. Implementing targeted provider education and health information technology-based CDS tools could help address knowledge gaps about current guidelines for evaluating hypercalcemia and when to refer for specialist care. Quality improvement initiatives aimed at increasing awareness, simplifying diagnostic algorithms, and facilitating access to surgery may lead to substantial improvements in long-term patient outcomes. Closing these gaps, however, will require a concerted, system-wide effort to optimize every step of the diagnostic and treatment pathway with the patient's perspective in mind.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-128/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-128/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-128/coif). D.W.B. reports grants and personal fees from EarlySense, personal fees from CDI Negev, equity from ValeraHealth, equity from Clew, equity from MDClone, personal fees and equity from AESOP, personal fees and equity from FeelBetter, personal fees and equity from Guided Clinical Solutions and grants from IBM Watson Health, all outside the submitted work. J.B.L. received the Brigham and Women's Hospital Department of Surgery 2023 Bruce A. Beal and Robert L. Beal Surgical Fellowship, which supported this work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As a retrospective review of pre-existing medical record data, the Mass General Brigham Institutional Review Board determined the study to be exempt from oversight (protocol No. 2022P002634) and waived the requirement for informed consent.

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