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Preoperative parathyroid hormone concentration predicts postoperative hypocalcemia severity in dogs undergoing parathyroidectomy

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Objective
To evaluate preoperative parathyroid hormone (PTH) concentration as a predictor of moderate to severe postoperative hypocalcemia following parathyroidectomy in dogs with primary hyperparathyroidism.

Methods
Retrospective analysis of dogs undergoing parathyroidectomy for primary hyperparathyroidism and excluding dogs receiving prophylactic calcitriol. Preoperative serum PTH measurement was stratified into groups by multiples of the assay-specific upper limit of normal (ULN). Whole blood ionized calcium (iCa) nadir was used to classify postoperative outcome, with moderate to severe hypocalcemia defined as iCa < 1.00 mmol/L.

Results
92 dogs were included. Moderate to severe hypocalcemia occurred in 36 dogs (39.1%). A graded relationship was identified between PTH strata and moderate to severe hypocalcemia: 9 of 47 dogs (19.1%) with normal PTH, 14 of 27 (51.9%) with > 1 to 2 times ULN, 5 of 10 (50.0%) with > 2 to 3 times ULN, and 8 of 8 (100%) with > 3 times ULN. A PTH cutoff of 1.05 times ULN yielded an area under the curve of 0.76 (95% CI, 0.65 to 0.86), with 72.2% sensitivity and 71.4% specificity. Median time to overall calcium nadir was 65.8 hours (range, 3.7 to 19,794.1), with 40 of 92 dogs (43.5%) reaching nadir after 72 hours. Late nadirs were common in dogs with moderate to severe hypocalcemia (25 of 36 [69.4%]) versus normocalcemia (10 of 44 [22.7%]).

Conclusions
Preoperative PTH concentration stratified by ULN multiples demonstrates a graded relationship with postoperative hypocalcemia.

Clinical Relevance
PTH-based stratification could identify high-risk patients warranting prophylactic therapeutics and extended monitoring.

Keywords: parathyroid, parathyroidectomy, calcium, hypocalcemia, canine

Primary hyperparathyroidism (PHPT) is an infrequent cause of hypercalcemia in dogs, typically resulting from an autonomously hypersecreting parathyroid adenoma and less commonly parathyroid hyperplasia or carcinoma.[1–5] The established definitive treatment for PHPT is open parathyroidectomy, which resolves hypercalcemia in the majority of cases.[6–8]

Disturbances in calcium homeostasis are a recognized complication of open parathyroidectomy. The pathophysiology of severe postoperative hypocalcemia involves "hungry bone syndrome," in which preoperative parathyroid hormone (PTH) concentration correlates with greater bone turnover and thus larger calcium deficits upon tumor removal. Abrupt PTH withdrawal results in unopposed osteoblast activity and rapid skeletal calcium deposition.[9]

The reported incidence of postoperative hypocalcemia in dogs with PHPT varies between 6.7% and 71%, reflecting differences in biochemical thresholds used to define hypocalcemia.[2,3,7,8,10–16] Clinical hypocalcemia, when specifically evaluated, is reported in only 8.3% to 17% of cases.[2,3,7,8,10,14,16] Postoperative hypocalcemia typically occurs within 7 days after surgery, though cases have been documented as late as 55 days postoperatively.[2,3,14] Currently, there is no consensus regarding appropriate indications for prophylactic calcitriol or calcium supplementation, and

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veterinary studies[3,4,15] have not consistently demonstrated a protective association between empiric calcitriol therapy and postoperative hypocalcemia.

Prior studies[3,4,8,13–15] have yielded conflicting results regarding predictors of postoperative hypocalcemia, with preoperative serum calcium concentrations demonstrating inconsistent associations with postoperative outcomes. The predictive value of preoperative PTH concentration has been less extensively investigated. Arbaugh et al[15] found no predictive value of preoperative PTH level in a cohort of 17 dogs, whereas larger studies by Milovancev and Schmiedt[14] and Travail et al[13] demonstrated significant associations between elevated PTH and the development of postoperative hypocalcemia. These findings parallel human PHPT literature, where preoperative PTH concentration is recognized as a significant predictor of postoperative hypocalcemia.[17–19]

Many previous studies[2,4,6,10,12–14,20] characterizing postoperative calcium trajectories have focused on only the first 48 to 72 hours after parathyroidectomy. Recent studies[2,10,21] have increasingly relied on decentralized outpatient monitoring through referring veterinarians, which may introduce variability in monitoring consistency and sample handling protocols.

No consensus criteria for hypocalcemia severity have been established in the veterinary literature, and studies have employed thresholds ranging from below the lower reference interval to specific cutoffs of < 1.2, < 1.12, < 1.1, or < 1.0 mmol/L.[2,3,8,13,22] Coady et al[22] proposed a classification system defining mild hypocalcemia as ionized calcium (iCa) 1.00 to 1.17 mmol/L and moderate to severe hypocalcemia as < 1.00 mmol/L based on clinical significance, though this framework has not been uniformly adopted.

The primary objective of this study was to evaluate preoperative PTH concentration, stratified by multiples of the assay-specific upper limit of normal (ULN), as a predictor of moderate to severe postoperative hypocalcemia (iCa < 1.00 mmol/L) following parathyroidectomy in dogs with PHPT. The secondary objective of this study was to characterize the temporal pattern of postoperative iCa decline, specifically whether the calcium nadir occurs beyond the commonly used 72-hour postoperative monitoring window.

Methods

Case selection

Electronic medical records from a single small-animal specialty hospital in Manchester, Missouri, were retrospectively reviewed to identify dogs that underwent cervical exploration with identification and excision of abnormal parathyroid tissue for PHPT. The study period extended from January 1, 2018, through June 30, 2024.

Inclusion criteria were dogs with confirmed PHPT, a preoperative PTH panel from the Michigan State University (MSU) Endocrinology Laboratory obtained prior to surgery, unilateral or bilateral parathyroidectomy, histopathology results, and at least 2 in-hospital postoperative iCa measurements. Primary hyperparathyroidism was diagnosed based on documented elevated iCa (> 1.40 mmol/L) together with an inappropriately normal or increased PTH concentration measured by the MSU Endocrinology Laboratory and a negative parathyroid hormone–related peptide result when available.

Patients were excluded for the following reasons: incomplete medical records; administration of bisphosphonates or corticosteroids prior to surgery; a diagnosis of hyperadrenocorticism; a diagnosis or suspicion of chronic kidney disease (creatinine > 1.6 mg/dL); initiation of calcitriol preoperatively, immediately postoperatively without a preceding iCa measurement, or while iCa was ≥ 1.12 mmol/L; and cases in which all in-hospital iCa measurements were above the reference interval (> 1.40 mmol/L).

Medical record review

The data collected included signalment, body weight, preoperative PTH panel measurements, pre- and postoperative iCa measurements, number of parathyroid glands excised, histopathology results, perioperative surgical complications, clinical signs of hypocalcemia, calcium carbonate and calcitriol and calcium gluconate administration, duration of hospitalization, and follow-up records when available.

Surgery

All surgeries were performed by either veterinarians with practice limited to surgery, board-certified surgeons, or residents under direct board-certified surgeon supervision using a standardized ventral cervical approach.[23] Abnormal parathyroid gland identification was based on intraoperative assessment of appearance, size, and consistency. Complete excision was confirmed by visual inspection and histopathological examination. Anesthetic protocols and postoperative care were determined at the discretion of the attending clinician.

Postoperative management

For each case, all iCa measurements obtained during the immediate postoperative hospitalization were collected with exact time stamps from electronic hospitalization flow-sheet documentation. Clinical signs of hypocalcemia documented during hospitalization were recorded together with the approximate time of occurrence. Clinical signs considered consistent with hypocalcemia included tremors, muscle fasciculations, facial rubbing or pruritis, weakness, unusual anxious or restless behavior, and seizures.[14,22] The first postoperative measurement was obtained within 24 hours of extubation, with subsequent measurements at approximately 12- to 24-hour intervals.

Calcitriol, oral calcium supplementation, and IV calcium gluconate were recorded as binary variables in conjunction with the iCa measurement immediately preceding the first dose. The initial dose was recorded for each medication; calcitriol was standardized to a 24-hour dose (ng/kg, q 24 h) to account for variation in dosing frequency across patients. These interventions were initiated with clinician discretion based on the degree and trajectory

of iCa concentration decline; no standardized institutional protocol dictated supplementation thresholds.

Laboratory methods and definitions

All PTH samples were derived from serum and submitted either directly to MSU or through third-party commercial laboratories (Antech Diagnostics, IDEXX Laboratories) that utilized MSU as their reference laboratory for canine PTH analysis. During the study period, the MSU endocrinology laboratory's PTH assay transitioned from a 2-site immunoradiometric assay (IRMA; reference interval, 0.5 to 5.8 pmol/L) to a chemiluminescent immunometric assay (CLIA; reference interval, 1.1 to 10.6 pmol/L) in May 2021. To account for this methodological change, PTH concentrations were normalized to multiples of the assay-specific ULN prior to stratification: samples obtained before May 26, 2021, were classified using ULN = 5.8 pmol/L, whereas those obtained after this date used ULN = 10.6 pmol/L. Both assays have been validated for canine samples with demonstrated precision (intra-assay coefficients of variation ≤ 7%).[24,25]

To enable comparison across assay types, raw PTH values were normalized by dividing by the assay-specific ULN to generate a unitless fold-to-upper limit of normal (fold-ULN) ratio. This ratio was standardized into 4 strata. Normal was defined as a value within the normal reference interval for either assay, > 1 to 2 times ULN was defined as > 5.8 to 11.6 pmol/L for the IRMA and > 10.6 to 21.2 pmol/L for the CLIA, > 2 to 3 times ULN was defined as > 11.6 to 17.4 pmol/L for the IRMA and > 21.2 to 31.8 pmol/L for the CLIA, and > 3 times ULN was defined as > 17.4 pmol/L for the IRMA and > 31.8 pmol/L for the CLIA.

During hospitalization, all iCa measurements were obtained on the same point-of-care handheld blood analyzer (i-STAT; Abbott Point of Care Inc) with venous whole-blood samples analyzed immediately without additional temperature correction. The institutional analyzer reference interval for dogs was 1.12 to 1.40 mmol/L, consistent with the manufacturer's recommended reference range. Preoperative iCa was defined as the most recent iCa measurement prior to surgery, obtained either from the institutional i-STAT analyzer or the hypercalcemia of malignancy panel performed by MSU.

Time origin for all time-dependent analyses was standardized to extubation after parathyroidectomy. Duration of hospitalization was defined as the interval from extubation to the time stamp of the last iCa measurement obtained prior to discharge.

The index hospitalization was defined as the postoperative hospitalization immediately following parathyroidectomy. Dogs whose last iCa measurement prior to discharge and first iCa measurement upon readmission were within 24 hours were considered a continuation of the index hospitalization for the purposes of iCa data collection.

The in-hospital nadir was defined as the lowest iCa measurement recorded during the index postoperative hospitalization. Overall nadir was defined as the lowest iCa measurement recorded at any point postoperatively across all available follow-up measurements. Calcium outcome was classified by overall nadir into 3 strata: normocalcemia (≥ 1.12 mmol/L), mild hypocalcemia (≥ 1.00 to < 1.12 mmol/L), and moderate to severe hypocalcemia (< 1.00 mmol/L). The moderate to severe threshold was selected based on previously published criteria identifying < 1.00 mmol/L as the cutoff for moderate to severe hypocalcemia.[22]

Follow-up data were assessed with outcomes classified based on calcium status and calcitriol requirements. All dogs with available follow-up had at least 1 posthospitalization iCa measurement obtained from whole blood using the institutional analyzer and documentation from at least 1 follow-up visit. Dogs that required no calcitriol or short-term calcitriol (defined as < 2 months) were classified as having a normal recovery. Dogs that required calcitriol administration for ≥ 2 months were classified as having prolonged calcitriol administration.[8]

Statistical analysis

The primary analysis evaluated the association between preoperative PTH strata and postoperative calcium outcome. The primary analysis comprised a single omnibus comparison of calcium outcome distribution across 4 PTH strata (χ^2 test). Secondary analyses included receiver operating characteristic curve analysis of PTH fold-ULN as a predictor of moderate to severe hypocalcemia, logistic regression modeling, and characterization of the temporal pattern of postoperative iCa decline. Associations between PTH strata and baseline demographics, treatment variables, and hospitalization duration were considered descriptive.

Normality was assessed for each continuous variable across the full cohort using the Shapiro-Wilk test. Descriptive statistics were reported with mean with SD if the assumption of normality was met, median with range if the assumption of normality was not met, and count with percentage for categorical data.

Group comparisons for continuous variables were performed using 1-way ANOVA with Tukey honestly significant difference post hoc analysis for normally distributed data and Kruskal-Wallis testing with pairwise Mann-Whitney *U* tests for non–normally distributed data. Associations between PTH strata and categorical outcomes were assessed using χ^2 testing with post hoc pairwise Fisher exact tests. Paired comparisons were evaluated with the paired *t* test when normality of differences was confirmed. Pearson correlation coefficients assessed relationships between continuous variables.

Receiver operating characteristic curve analysis evaluated the predictive accuracy of preoperative PTH measurements, expressed as a fold of the assay-specific ULN (fold-ULN), for moderate to severe postoperative hypocalcemia (< 1.00 mmol/L). The area under the curve (AUC) 95% CI was estimated using the Hanley-McNeil method. The optimal cutoff was determined using the Youden index (J = sensitivity + specificity − 1). Binary logistic regression

quantified the association between preoperative PTH fold-ULN and binary outcomes (moderate to severe hypocalcemia and calcitriol administration), with results reported as ORs with 95% CIs.

To evaluate whether the rate of postoperative iCa decline differed among PTH groups, a linear mixed-effects model was fit to repeated iCa measurements obtained during the first 168 postoperative hours. The model included random intercepts for individual dogs to account for within-subject correlation of repeated measurements. Fixed effects included time from extubation (hours), PTH group, and their interaction. The normal PTH group served as the reference category. Dogs with fewer than 3 in-hospital iCa measurements were excluded from this analysis. Other than the linear mixed-effects model, analyses were performed on available data for each variable; no imputation was performed for missing values.

All final analyses were performed using Python (version 3.11; Python Software Foundation) with the *scipy* (version 1.16.3), *statsmodels* (version 0.14.6), and *scikit-learn* (version 1.8.0) libraries. Preliminary analyses were performed using Jamovi (version 2.7.17; The Jamovi Project). Significance was set at $\alpha = .05$ (2 tailed) for all tests.

Results

Study population

Ninety-two dogs met inclusion criteria. There were 53 castrated males (57.6%), 37 spayed females (40.2%), and 2 intact males (2.2%) included. The mean age was 11.2 years (SD, 2.4). The median body weight was 13.8 kg (range, 4.3 to 55.9 kg). Mixed-breed dogs accounted for 38 of 92 dogs (41.3%); the most common pure breeds were Dachshund (11 of 92 [12%]), Shih Tzu (11 of 92 [12%]), and Beagle (7 of 92 [7.6%]).

The preoperative iCa concentration was measured a median of 0 days prior to surgery (range, 0 to 12 days). The majority of preoperative iCa measurements (87 of 92 [94.6%]) were obtained on the day of surgery with the institutional i-STAT analyzer. In 5 of 92 cases (5.4%), preoperative iCa measurements were obtained within 12 days prior to surgery with the institutional i-STAT analyzer. Two of 92 cases (2.2%) utilized serum iCa concentrations recorded from the hypercalcemia of malignancy panel performed at MSU. The median panel iCa was 1.72 mmol/L (range, 1.37 to 2.38 mmol/L), and the median preoperative iCa was 1.68 mmol/L (range, 1.37 to 2.41 mmol/L). Paired differences were normally distributed (Shapiro-Wilk $W = 0.977$; $P = .11$), with no significant differences between panel and preoperative iCa concentrations (95% CI of mean difference, −0.03 to 0.03 mmol/L; $P = .75$).

Parathyroid hormone concentration was measured in all dogs, with a median of 7.7 pmol/L (range, 1.4 to 99.5 pmol/L), and was obtained a median of 42 days prior to surgery (range, 1 to 240 days). Forty-eight of 92 dogs (52.2%) had the IRMA assay (median, 4.65 pmol/L; range, 1.4 to 21.9), and 44 of 92 (47.8%) had the CLIA assay (median, 12.45 pmol/L; range, 2.9 to 99.5).

When stratified by multiples of the assay-specific ULN, PTH distribution was normal in 47 of 92 (51.1%), > 1 to 2 times ULN in 27 of 92 (29.3%), > 2 to 3 times ULN in 10 of 92 (10.9%), and > 3 times ULN in 8 of 92 (8.7%; **Table 1**).

Surgical outcomes

Fifty of 92 dogs (54.3%) had a single gland removed, 38 of 92 (41.3%) had 2 glands removed, and 4 of 92 (4.3%) had 3 glands removed. A total of 138 excised tissue specimens were submitted for histopathologic examination. Of these, 121 of 138 (87.7%) were confirmed as abnormal parathyroid tissue: adenoma (87 of 138 [63.0%]), hyperplasia (11 of 138 [8.0%]), carcinoma (11 of 138 [8.0%]), and benign indeterminate parathyroid lesions (12 of 138 [8.7%]). The remaining 17 of 138 (12.3%) were histopathologically normal parathyroid tissue (6 of 138 [4.3%]) or nonparathyroid tissue (11 of 138 [8.0%]). Complete histopathologic excision was evaluable in 90 of 92 patients (97.8%) and confirmed in 89 of 90 (98.9%).

No major surgical complications were recorded during the perioperative period.

The median hospitalization was 2.8 days (range, 0.6 to 10.6 days). All dogs survived to discharge.

Calcium outcomes

A total of 635 index hospitalization postoperative iCa measurements were obtained after the initial presurgical measurement (median, 6/patient; range, 2 to 21). Two dogs were discharged and readmitted within 24 hours, and their iCa measurements were included as part of the index hospitalization. The median in-hospital nadir iCa was 1.12 mmol/L (range, 0.61 to 1.44 mmol/L).

Overall nadir incorporated all available postoperative iCa measurements; these were obtained on the institutional i-STAT analyzer in 91 of 92 dogs (98.9%). One dog had a follow-up iCa measurement obtained from whole blood on an external analyzer (Element; Heska), which was included in the analysis. The overall median nadir iCa was 1.1 mmol/L (range, 0.53 to 1.39 mmol/L). The in-hospital nadir was equivalent to the overall nadir in 61 of 92 dogs (66.3%). In 31 of 92 dogs (33.7%), calcium continued to decline after discharge, with an additional median drop of 0.15 mmol/L (range, 0.01 to 0.52 mmol/L). The in-hospital nadir correlated strongly with the overall nadir ($r = 0.82$; $P < .001$).

Postoperative calcium outcomes were distributed as follows: normocalcemia in 44 of 92 (47.8%), mild hypocalcemia in 12 of 92 (13%), and moderate to severe hypocalcemia in 36 of 92 (39.1%). Body weight differed significantly across both PTH strata (Table 1) and calcium outcome groups **(Table 2)**.

Clinical signs consistent with hypocalcemia were observed in 17 of 92 dogs (18.5%) during hospitalization; 13 of 17 (76.5%) had moderate to severe biochemical hypocalcemia. Including owner-provided history at follow-up visits, 28 of 48 dogs (58.3%) with biochemical hypocalcemia exhibited clinical signs, of which 27 of 28 (96.4%) had moderate to severe hypocalcemia.

Table 1—Comparison of clinical and biochemical variables by preoperative parathyroid hormone (PTH) concentration relative to the assay-specific upper limit of normal (ULN) in 92 dogs undergoing parathyroidectomy for primary hyperparathyroidism at a single institution (2018 through 2024).

	Normal PTH	1–2 times ULN	2–3 times ULN	> 3 times ULN	*P* value
n	47 (51.1%)	27 (29.3%)	10 (10.9%)	8 (8.7%)	—
Age (y)*	11.3 (2.3)	11.0 (2.5)	10.8 (2.8)	11.9 (1.8)	.70
Weight (kg)†	17.7 (4.35–5.9)	10.7 (4.8–43.2)	22.2 (8.9–32.7)	7.6 (4.3–28.8)	.02
Sex‡		.98			
Female spayed	18	12	4	3	—
Male neutered	28	14	6	5	—
Male intact	1	1	0	0	—
Preoperative iCa (mmol/L)†	1.62 (1.37–2.02)[a,b]	1.8 (1.43–2.25)[a]	1.85 (1.53–2.26)[b]	1.85 (1.44–2.41)	< .001
iCa overall nadir (mmol/L)†	1.18 (0.53–1.38)[a,b]	0.99 (0.66–1.39)[a,c]	0.98 (0.73–1.29)[d]	0.7 (0.56–0.98)[b-d]	< .001
Calcium outcome‡		< 0.001			
Normocalcemia (> 1.12 mmol/L)	33 (70.2%)	7 (25.9%)	4 (40%)	0	—
Mild hypocalcemia (1.0–1.12 mmol/L)	5 (10.6%)	6 (22.2%)	1 (10%)	0	—
Severe hypocalcemia (< 1.0 mmol/L)	9 (19.1%)	14 (51.9%)	5 (50%)	8 (100%)	—
Time to overall nadir (h)†	55.1 (3.7–16,246.2)	78 (11.6–19,794.1)	75 (40.8–7,023)	143.2 (29.8–1,244.3)	.157
Nadir > 72 h‡	15 (31.9%)	14 (51.9%)	5 (50%)	6 (75%)	.081
Median iCa decline (mmol/L)†,§	0.46 (0.09–1.31)[a-c]	0.77 (0.3–1.45)[a,d]	0.87 (0.44–1.4)[b]	1.26 (0.6–1.51)[c,d]	< .001
Calcitriol administration‡	8 (17%)[a,b]	11 (40.7%)[a,c]	4 (40%)	7 (87.5%)[b,c]	< .001
Calcium gluconate administration‡	5 (10.6%)[a]	2 (7.4%)[b]	1 (10%)	4 (50%)[a,b]	.013
Calcium carbonate administration‡	8 (17%)[a]	6 (22.2%)[b]	3 (30%)[c]	7 (87.5%)[a-c]	< .001
Hospitalization duration (d)†	2.6 (0.6–8.2)[a,b]	3.8 (0.86–6.7)[a]	4.2 (2.2–10.6)[b]	3 (1.2–5.1)	.001

PTH groups are defined relative to the ULN for the specific assay used: immunoradiometric assay (n = 48; ULN = 5.8 pmol/L) or chemiluminescent immunoassay (44; ULN = 10.6 pmol/L).

*Values reported as mean (SD), analyzed via 1-way ANOVA. †Values reported as median (range), analyzed via Kruskal-Wallis test with post hoc pairwise comparisons performed with the Mann-Whitney *U* test. ‡Values reported as number of dogs and percentage of total dogs in group, analyzed via χ^2 test, with post hoc pairwise comparisons performed with the Fisher exact test. §Median iCa decline = preoperative iCa − nadir (mmol/L).

iCa = Ionized calcium.

[a–d]Values differ significantly ($P < .05$) on post hoc pairwise comparisons.

Table 2—Comparison of clinical and biochemical variables by calcium outcome group for the 92 dogs described in Table 1.

	Normocalcemia (≥ 1.12 mmol/L)	Mild hypocalcemia (1.0–1.11 mmol/L)	Severe hypocalcemia (< 1.0 mmol/L)	*P* value
n	44 (47.8%)	12 (13.0%)	36 (39.1%)	—
Age (y)*	11.3 (2.5)	10.1 (2.6)	11.4 (2.1)	.21
Weight (kg)†	18.6 (4.4–55.9)	12.3 (6.9–36.3)	10.2 (4.3–39.4)	.006
Preoperative iCa (mmol/L)†	1.65 (1.37–2.26)	1.68 (1.43–2.05)	1.76 (1.43–2.41)	.072
PTH (pmol/L)†	5.4 (1.4–29.4)[a]	6.9 (2.4–22.9)	12.3 (2.2–99.5)[a]	< .001
PTH (fold-ULN)†	0.79 (0.24–2.77)[a]	1.1 (0.35–2.2)	1.3 (0.38–9.4)[a]	< .001
Calcium overall nadir (mmol/L)†	1.22 (1.12–1.39)	1.08 (1.0–1.11)	0.84 (0.53–0.99)	< .001
Time to overall nadir (h)†	50.0 (3.7–352)	55.4 (11.6–262.4)	113.6 (29.8–19,794.1)	< .001
Nadir > 72 h‡	10 (22.7%)	5 (41.7%)	25 (69.4%)	< .001
Median iCa decline (mmol/L)†,§	0.44 (0.09–1)	0.6 (0.35–0.96)	1.01 (0.51–1.51)	< .001
Calcitriol administration‡	0 (0%)	0 (0%)	30 (83.3%)	< .001
Calcium gluconate administration‡	0 (0%)	0 (0%)	12 (33.3%)	< .001
Calcium carbonate administration‡	0 (0%)	1 (8.3%)	23 (63.9%)	< .001
Hospitalization duration (d)†	2.2 (0.6–5.5)[a,b]	3 (1.8–4.7)[a]	3.8 (1.2–10.6)[b]	< .001

*Values reported as mean (SD), analyzed via 1-way ANOVA. †Values reported as median (range), analyzed via Kruskal-Wallis test with post hoc pairwise comparisons performed with the Mann-Whitney *U* test. ‡Values reported as number of dogs and percentage of total dogs in group, analyzed via χ^2 test, with post hoc pairwise comparisons performed with the Fisher exact test. §Median iCa decline = preoperative iCa – nadir (mmol/L).

fold-ULN = Preoperative PTH concentration divided by the assay-specific upper limit of normal.

[a,b]Values differ significantly ($P < .05$) on post hoc pairwise comparisons.

Oral calcium carbonate was administered to 24 of 92 cases (26.1%; median, 73.9 mg/kg; range, 28.4 to 177.5). Oral calcitriol was administered to 30 of 92 dogs (32.6%; median, 33.8 ng/kg, q 24 h; range, 14.6 to 98.0) and initiated at a median iCa of 0.91 mmol/L (range, 0.66 to 1.08 mmol/L). Intravenous calcium gluconate was required in 12 of 92 dogs (13%; median, 65.5 mg/kg; range, 15.1 to 110.2) and initiated at a median iCa of 0.77 mmol/L (range, 0.53 to 0.97 mmol/L). All dogs who received IV calcium gluconate also received calcitriol.

PTH association with calcium outcomes

The distribution of calcium outcomes differed significantly among PTH strata (χ^2 = 28.4; P < .001; **Figure 1**). Moderate to severe hypocalcemia occurred in 9 of 47 dogs (19.1%) with normal PTH, 14 of 27 (51.9%) with > 1 to 2 times ULN, 5 of 10 (50.0%) with > 2 to 3 times ULN, and 8 of 8 (100%) with > 3 times ULN.

When PTH concentration was analyzed as a continuous variable, it differed significantly among calcium outcome groups (H = 15.57; P < .001), with dogs with moderate to severe hypocalcemia having higher PTH concentrations than normocalcemic dogs (U = 395.0; P < .001); no other pairwise comparisons reached significance. This pattern was similar when PTH concentration was expressed as a continuous fold-ULN value (H = 19.34; P < .001), with only the pairwise comparison between moderate to severe hypocalcemia and normocalcemia groups reaching significance (U = 336.0; P < .001; **Figure 2**).

To enable comparison across assay types, receiver operating characteristic analysis was performed using PTH expressed as a fold-ULN **(Figure 3)**. This analysis yielded an AUC of 0.76 (95% CI, 0.65 to 0.86), with an optimal cutoff of 1.05 times ULN (Youden J = 0.44; equivalent to 6.1 pmol/L for the IRMA and 11.1 pmol/L for the CLIA). At this threshold, sensitivity was 72.2%, and specificity was 71.4%. On logistic regression using fold-ULN as a continuous predictor, for each 1X ULN increase in preoperative PTH, the odds of moderate to severe hypocalcemia increased 3-fold (OR, 3.0; 95% CI, 1.54 to 5.82; P = .001). In contrast, while preoperative iCa concentration differed significantly across PTH strata (H = 16.53; P < .001; Table 1), it did not differ significantly among calcium outcome groups (Table 2) and therefore was not further evaluated as a predictor.

The proportion of dogs receiving calcium carbonate, calcitriol, and calcium gluconate differed significantly across PTH strata (Table 1). Preoperative PTH fold-ULN was a significant predictor of calcitriol administration on logistic regression (OR, 2.32; 95% CI, 1.35 to 3.99; P = .002).

Temporal patterns of calcium decline

All dogs experienced a postoperative decline in iCa concentration **(Figure 4)**. The median time to in-hospital nadir was 52.9 hours (range, 2.3 to 208.5 hours), whereas the median time to overall nadir was 65.8 hours (range, 3.7 to 19,794.1 hours). Forty of 92 dogs (43.5%) reached their overall

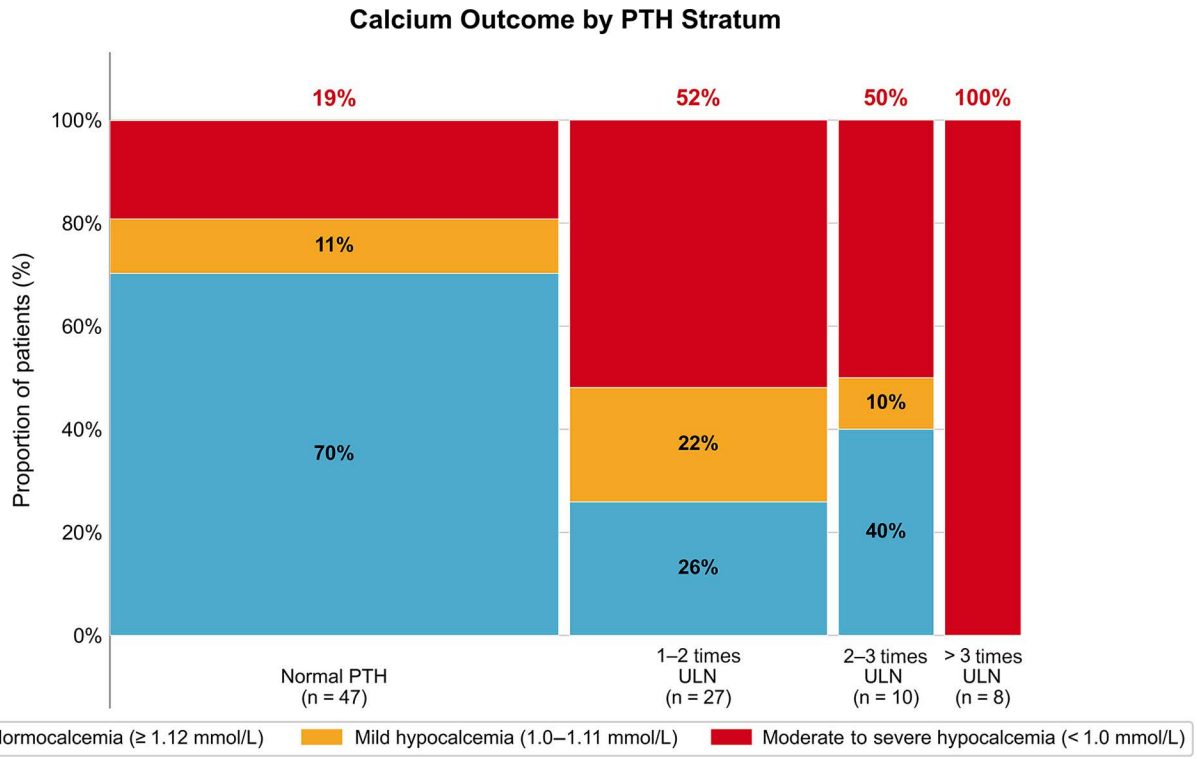

Figure 1—Ninety-two dogs undergoing parathyroidectomy for primary hyperparathyroidism at a single institution (2018 through 2024) were stratified by preoperative parathyroid hormone (PTH) concentration expressed as multiples of the assay-specific upper limit of normal (ULN). Stacked mosaic bar graph demonstrating proportion of patients in each overall nadir calcium outcome group stratified by PTH stratum.

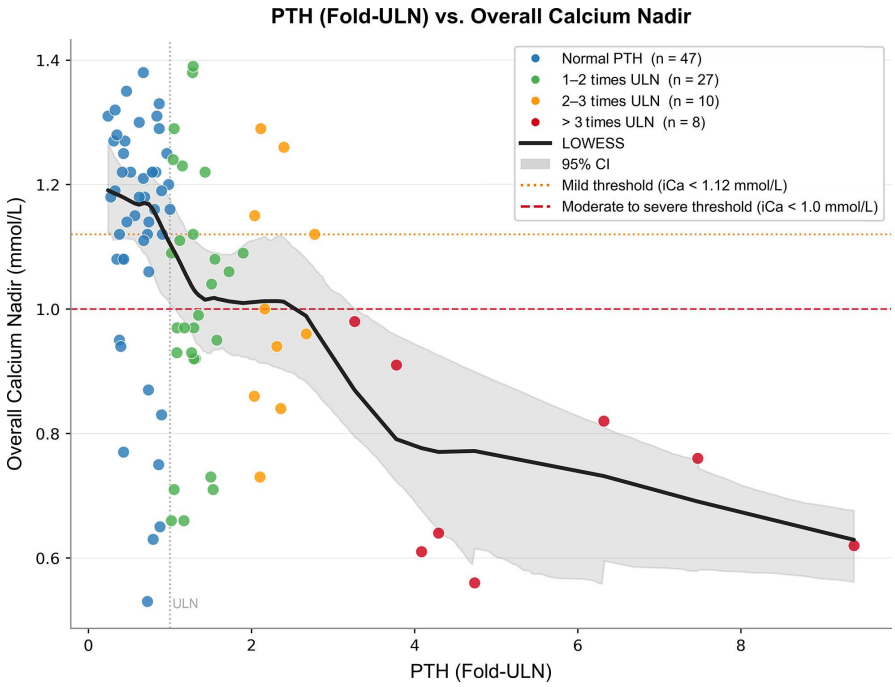

Figure 2—For the 92 dogs described in Figure 1, the relationship between preoperative PTH concentration (expressed as multiples of the assay-specific ULN) and overall postoperative ionized calcium (iCa) nadir. Each point represents 1 dog, color-coded by PTH stratum. The solid black line represents the locally weighted scatterplot smoothing (LOWESS) trend, and the gray shaded region represents the bootstrapped 95% CI.

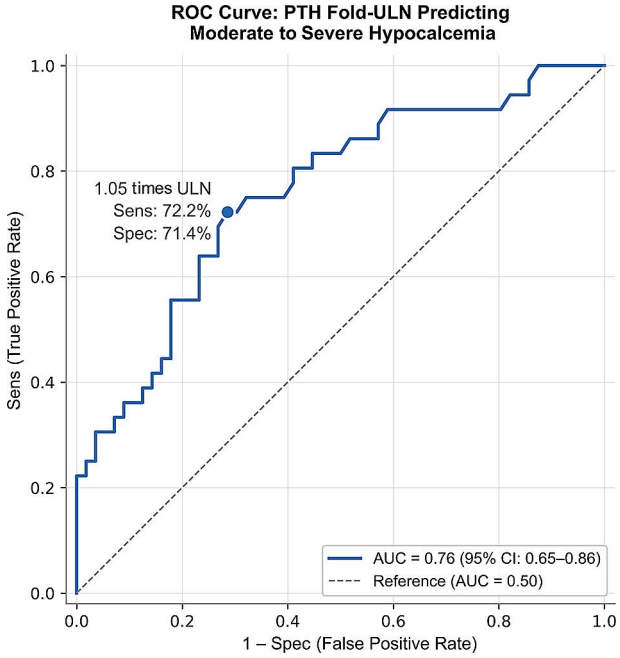

Figure 3—For the 92 dogs described in Figure 1, the receiver operator characteristic (ROC) curve analysis of preoperative plasma PTH concentration as a predictor of moderate to severe postoperative hypocalcemia (< 1.00 mmol/L). Raw PTH values were normalized by dividing by the assay-specific ULN to generate a unitless fold-to-ULN ratio. The area under the curve (AUC) of 0.76 (95% CI, 0.65 to 0.86) corresponded to an optimal cutoff of 1.05 times ULN and a sensitivity (Sens) of 72.2% and specificity (Spec) of 71.4%.

nadir after 72 hours postoperatively. The proportion reaching overall nadir beyond 72 hours differed significantly by calcium outcome group: 10 of 44 normocalcemia (23%), 5 of 12 mild hypocalcemia (42%), and 25 of 36 moderate to severe hypocalcemia (69%; $\chi^2 = 17.60$; $P < .001$).

The magnitude of iCa decline from the preoperative value to the overall nadir differed significantly among PTH groups ($H = 30.21$; $P < .001$). Dogs with normal PTH concentrations (47 of 92) had a smaller decline than dogs with elevated PTH (45 of 92; $U = 384.0$; $P < .001$; Table 1).

In a linear mixed-effects model of repeated iCa measurements over the first 168 postoperative hours (n = 90; 619 observations; 2 dogs excluded for < 3 in-hospital measurements), iCa decreased significantly over time (coefficient = −0.0041 mmol/L/h; $z = -11.65$; $P < .001$). This corresponds to an approximate decline of 0.1 mmol/L/d. The > 3 times ULN group demonstrated a significantly steeper rate of iCa decline compared to the normal PTH group (coefficient = −0.0015 mmol/L/h; $z = -2.06$; $P = .04$), which corresponds to an approximate decline of 0.13 mmol/L/d. Conversely, the 1 to 2 times ULN (coefficient = 0.0002 mmol/L/h; $z = 0.48$; $P = .63$) and 2 to 3 times ULN (coefficient = 0.0003 mmol/L/h; $z = 0.595$; $P = .55$) groups did not differ significantly from the normal group.

Calcium nadir, PTH, and hospitalization duration

Lower iCa nadir was correlated with longer hospitalization for both in-hospital ($r = -0.23$; $P = .028$) and overall nadir ($r = -0.30$; $P = .003$). Hospitalization duration differed significantly among calcium outcome groups ($H = 28.68$; $P < .001$), with dogs with moderate to severe hypocalcemia hospitalized longer than normocalcemic dogs ($U = 263.0$; $P < .001$; Table 2). Hospitalization also differed among PTH groups ($H = 15.48$; $P = .001$); dogs with normal PTH had shorter stays than those in the 1 to 2 times ULN ($U = 357.0$; $P = .002$) and 2 to 3 times ULN groups ($U = 95.0$; $P = .003$), whereas the > 3 times ULN group did

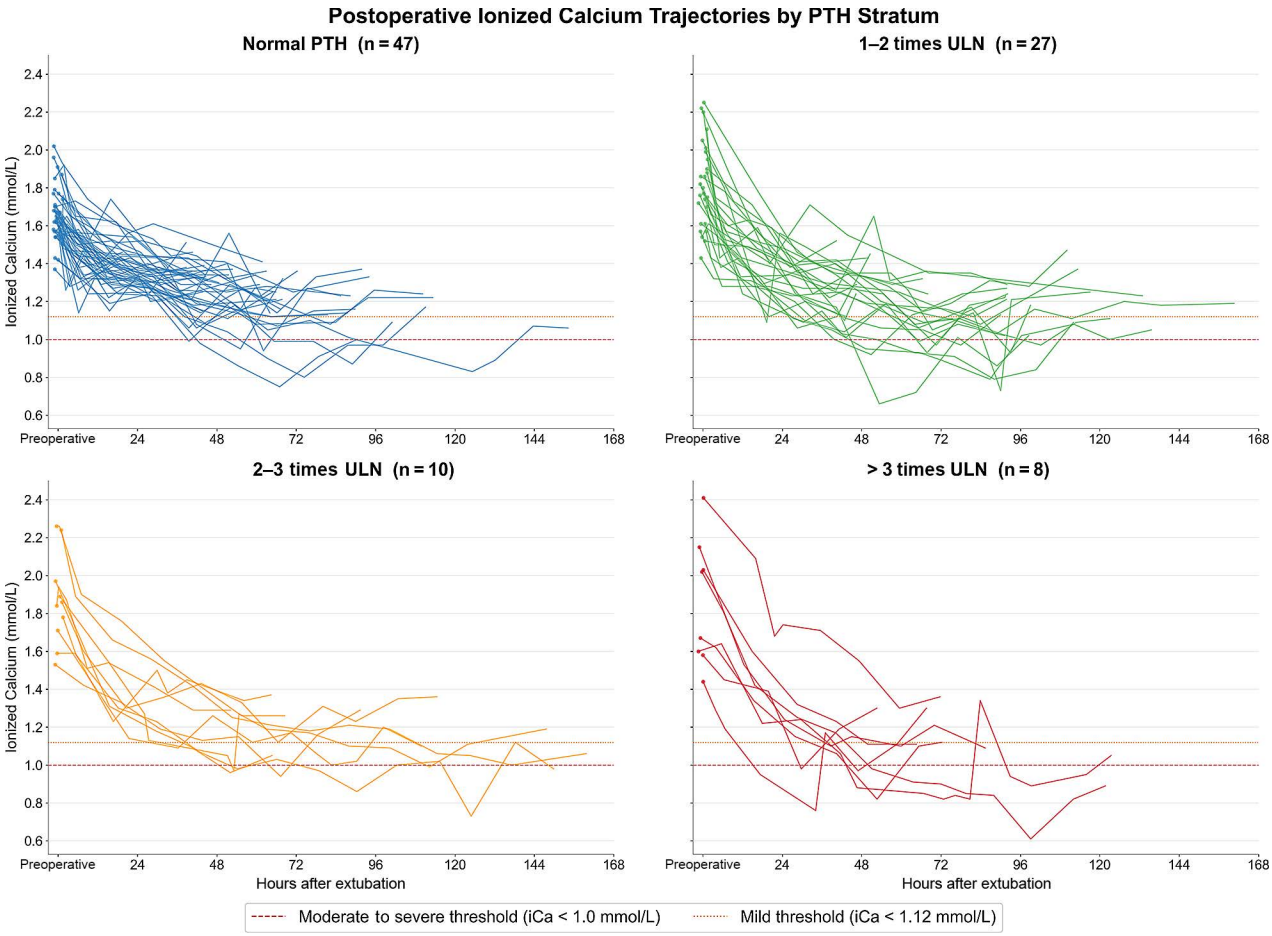

Figure 4—For the 90 dogs described in Figure 1 with ≥ 3 in-hospital iCa measurements, the postoperative hospitalized iCa trajectories by preoperative PTH stratum within the first 168 hours of hospitalization (n = 623 postoperative iCa readings). Each line represents 1 patient's iCa (mmol/L) over time (hours after extubation) within each PTH stratum. The scatter points on the far left of each plot indicate the preoperative iCa for each patient.

not differ significantly from the normal group (*P* = .103; Table 1).

Follow-up outcomes

Follow-up data were available for 80 of 92 dogs (87%). Dogs achieved normal recovery (no calcitriol or short-term calcitriol < 2 months) in 67 of 80 cases (83.8%), comprising 55 of 80 (68.8%) with complete resolution requiring no supplementation and 12 of 80 (15%) requiring only short-term calcitriol supplementation. Prolonged calcitriol administration (≥ 2 months) was required in 15 of 80 dogs (18.8%).

Discussion

The findings of this study demonstrate that preoperative PTH concentration, stratified by multiples of the assay-specific ULN, is a predictor of moderate to severe postoperative hypocalcemia in dogs undergoing parathyroidectomy for PHPT. A graded relationship was identified: moderate to severe hypocalcemia occurred in 19.1% of dogs with normal PTH, rising to approximately 50% in dogs with > 1 to 3 times ULN elevations and 100% of dogs with PTH > 3 times ULN. Additionally, by characterizing the postoperative calcium trajectory without the confounding effect of prophylactic calcitriol, we found that 43.5% of dogs reached their calcium nadir beyond 72 hours postoperatively, with dogs developing moderate to severe hypocalcemia disproportionately represented among late nadirs.

These findings are consistent with the significant association between preoperative PTH concentrations and postoperative hypocalcemia reported by Milovancev and Schmiedt[14] in 62 dogs and Travail et al[13] in 103 dogs. This contrasts with Arbaugh et al,[15] who found no predictive value of PTH concentrations in a smaller cohort of 17 dogs. Notably, our analysis employed PTH expressed as a fold of the assay-specific ULN rather than raw concentration, which accommodates interassay variability and may facilitate crossinstitutional application.

The optimal cutoff of 1.05 times ULN identified in our study is effectively at the upper boundary of the reference interval, suggesting that any PTH elevation above normal confers an increased risk of postoperative moderate to severe hypocalcemia. This threshold is not directly comparable to the absolute cutoff reported by Travail et al[13] (75 pg/mL or 7.95 pmol/L). Travail et al[13] defined hypocalcemia based on institution-specific reference intervals

in a multi-institutional cohort, whereas our analysis specifically targeted moderate to severe hypocalcemia (< 1.00 mmol/L) as defined by Coady et al.[22] This distinction is clinically meaningful: our threshold identifies the subset of patients most likely to require intervention as supported by our observation that 96% of dogs exhibiting clinical signs of hypocalcemia had iCa below 1.00 mmol/L. Additionally, the moderate discriminative performance (AUC, 0.76) with a sensitivity of 72.2% and specificity of 71.4% indicates that preoperative PTH fold-ULN is a useful but imperfect screening tool for the individual patient. However, the clinical utility of PTH may be better realized through stratified risk categories as the graded relationship between PTH strata and hypocalcemia severity provides risk profiles that can inform individualized perioperative planning—ranging from 19.1% in dogs with normal PTH to approximately 50% in dogs with > 1 to 3 times ULN and to 100% in dogs with > 3 times ULN (Figure 1).

The overall incidence of moderate to severe postoperative hypocalcemia was 39.1%, which falls within the broad range reported in the literature (6.7% to 71%) but exceeds rates reported by several studies.[2,3,7,8,10–16] This likely reflects differences in case selection and ascertainment methodology. Unlike studies employing prophylactic calcitriol supplementation—which may attenuate the calcium nadir—calcitriol in our cohort was administered only after hypocalcemia had developed, allowing the natural calcium trajectory to be observed before intervention. Furthermore, all dogs had at least 1 postdischarge iCa measurement obtained on the institutional analyzer, which helped to capture the 33.7% of dogs that reached their overall nadir after discharge.

Regarding the temporal pattern of postoperative calcium decline, 43.5% of dogs did not reach their lowest iCa measurement until after 72 hours postoperatively. This delayed nadir occurred disproportionately in dogs that developed moderate to severe hypocalcemia, with 69.4% reaching nadir after 72 hours compared to only 22.7% of normocalcemic dogs. In the linear mixed-effects model, iCa concentration decreased significantly over time in all dogs. A significantly steeper rate of decline was observed in the > 3 times ULN group, though this finding should be interpreted cautiously given the small subgroup size (n = 8) and warrants further investigation. These observations suggest that discharge timing should be guided by calcium trajectory rather than a fixed postoperative interval, particularly for patients with elevated PTH.

Beyond a binary cutoff, stratification of PTH by multiples of the ULN provides clinically actionable risk categories. Dogs with PTH > 3 times ULN represented a high-risk population: 100% developed moderate to severe hypocalcemia, 87.5% warranted calcitriol, and 75% reached nadir beyond 72 hours. In contrast, dogs with normal preoperative PTH levels required calcitriol in only 17% of cases and experienced significantly smaller iCa declines, suggesting conservative management with shorter hospitalization may be appropriate for this group. This graded relationship supports tailoring perioperative management intensity to individual patient risk rather than adhering to uniform prophylactic protocols, reserving aggressive intervention (prophylactic calcitriol, extended hospitalization, and close outpatient follow-up) for patients with markedly elevated PTH levels.

While beyond the scope of the objectives of this study, body weight differed significantly across both PTH strata and calcium outcome groups, with smaller dogs overrepresented in higher PTH groups and more severe hypocalcemia. This may reflect the known breed predisposition of smaller breeds to PHPT and may represent a confounding variable that was not controlled for in these analyses.

Several limitations of this study warrant consideration. The retrospective design introduces inherent biases in case selection and data availability. As a single-institution study, our findings may not generalize to practices with different surgical techniques, anesthetic protocols, or postoperative care practices. The absence of a concurrent cohort receiving prophylactic calcitriol precludes direct comparison of management strategies. Our exclusion of dogs with renal disease limits the ability to extrapolate these findings to dogs with concurrent renal dysfunction. Additionally, we relied on creatinine rather than or in addition to symmetric dimethylarginine, which may have led to the inclusion of patients with early, subclinical renal dysfunction. While we excluded patients receiving prophylactic calcitriol, the decision to initiate therapeutic calcitriol was at the clinician's discretion. Overall nadir included a single follow-up iCa measurement obtained on an external analyzer, introducing potential interinstrument variability for that patient. The > 3 times ULN group comprised only 8 dogs, and while the uniformity of outcomes in this group is striking, larger studies are needed to confirm these findings. Parathyroid hormone samples were obtained at variable intervals prior to surgery (median, 42 days; range, 1 to 240 days), and tumor progression during this interval could have affected the predictive relationship, though the consistency of our findings suggests this effect was minimal. Finally, the significant association between body weight and both PTH strata and calcium outcome groups may reflect breed predisposition rather than an independent predictive relationship, and the possibility of a type I error cannot be excluded.

Preoperative PTH concentration stratified by multiples of the reference interval upper limit may be a practical predictor of postoperative hypocalcemia severity following parathyroidectomy in dogs with PHPT. By characterizing the unmasked calcium trajectory, we demonstrated that moderate to severe biochemical hypocalcemia is common and often delayed beyond 72 hours. Dogs with PTH levels exceeding 3 times the ULN are at high risk for moderate to severe hypocalcemia requiring calcitriol supplementation, prolonged hospitalization, and potentially delayed calcium nadir beyond 72 hours. These findings support transitioning from uniform prophylaxis protocols toward precision medicine

approaches that tailor perioperative management intensity to individual patient risk profiles.

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This work is dedicated to Chief; a beloved friend whose legacy continues to help other pets and the people who love them.

Disclosures

Claude Sonnet 4.5 (Anthropic) was used to help optimize the grammar and clarity of the originally drafted manuscript.

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