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Ambidirectional cohort study on the agreement of ultrasonography and surgery in the identification of parathyroid pathology, and predictors of postoperative hypocalcemia in 47 dogs undergoing parathyroidectomy due to primary hyperparathyroidism

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Abstract

Objective: To investigate (1a) agreement of ultrasonographic, surgical, and histopathologic findings in the diagnosis of a neoplastic etiology underlying primary hyperparathyroidism (PHPT), (1b) the ability of ultrasonographically determined parathyroid gland size to distinguish between malignant (carcinoma) and non-malignant (hyperplasia, adenoma) pathology, and (2) variables associated with postoperative hypocalcemia in dogs undergoing surgical treatment of PHPT.

Study Design: Ambidirectional cohort study.

Animals: Forty-seven client owned dogs with PHPT (34 retrospective; 13 prospective).

Methods: Data were extracted from medical records. Method agreements were explored using Cohen's Kappa statistic. A receiver operating characteristic curve (ROC) was used to determine a cut-off separating parathyroid pathologies. Univariable and multivariable models assessed associations between postoperative hypocalcemia and potential risk factors.

Results: Agreement of ultrasound and surgery for number and side of affected glands was 31/47 (65.9%) and 34/47 (72.3%), respectively. In 37/47 (78.7%) cases, parathyroid tissue was correctly assessed as pathologic by the surgeon. An ultrasonographic cut-off of ≥8.0 mm (ROC AUC = 0.82) best distinguished malignant from benign pathologies. Dogs with a preoperative serum ionized calcium (iCa) concentration ≥1.75 mEq/L had 7.5 times greater odds of becoming hypocalcemic postoperatively.

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Conclusion: A fair agreement existed between ultrasonographic and surgical findings in dogs with PHPT. A parathyroid mass ≥8.0 mm on ultrasonographic examination was suggestive of malignancy, while dogs with a preoperative serum iCa concentration ≥1.75 mEq/L were at increased risk for postoperative hypocalcemia in this study.

Clinical significance: This study supports the use of bilateral cervical surgical exploration to identify abnormal parathyroid glands for the treatment of PHPT.

1 | INTRODUCTION

Primary hyperparathyroidism (PHPT) is a well-recognized cause of hypercalcemia in dogs.[1] Despite this, research surrounding PHPT remains contentious.[1–15] In PHPT, a hypercalcemic state is produced through the secretion of parathyroid hormone (PTH) by pathologic chief cells (adenoma, hyperplasia, or adenocarcinoma) resulting in stimulation of renal tubular and intestinal calcium resorption and osteoclast-mediated bone resorption.[16,17] Clinical signs of PHPT (polyuria and polydipsia, lethargy, muscle weakness, and general malaise) are useful in supporting a diagnosis, but are not pathognomonic.[2,8,9] Parathyroidectomy, as a treatment for PHPT, has proven to have an excellent cure rate of approximately 95%.[9,10,18] Despite the success of treatment, postoperative hypocalcemia remains a frustrating and unpredictable complication that occurs in approximately 38% of patients.[11]

Minimally invasive treatments for PHPT such as ultrasound-guided ablation with radiofrequency heat application or ethanol provide an attractive option for treatment.[12,13] However, these techniques have reported failure rates of up to 31% and 28%, respectively.[9,12] In addition, the potential for metastasis with parathyroid carcinomas, may make ultrasound guided ablation less desirable than surgical resection.[19,20] Cervical ultrasound is the most common imaging modality utilized for localization of abnormal glands and surgical planning of PHPT, however, ultrasonographic and surgical findings are often inconsistent.[3,10–12,21] Differences in identifying the side of the parathyroid pathology between these modalities has been reported in up to 19% of cases.[11] In addition, previous studies have sought to utilize ultrasonography to establish a size threshold that can help to differentiate hyperplastic parathyroid glands from parathyroid adenomas and carcinomas but failed to identify consistent and reliable cut-off values.[21,22] Poor agreement between ultrasonographic findings and parathyroid pathology may account for the decreased success rates of ultrasound guided ablation when compared with traditional parathyroidectomy.[10–12]

The first objective of this study was to determine the agreement of ultrasonographic, surgical, and histopathologic findings in the diagnosis of a neoplasm underlying PHPT, while also investigating the ultrasonographically determined parathyroid gland size that was best able to distinguish between malignant (carcinoma) and non-malignant (hyperplasia, adenoma) pathology. We hypothesized that there would be moderate agreement between diagnostic modalities and that parathyroid carcinomas would be larger than parathyroid adenomas and hyperplastic parathyroid glands. The second objective was to identify variables associated with postoperative hypocalcemia in dogs undergoing surgical treatment of PHPT. We hypothesized that severity of preoperative changes in calcium status are associated with postpartum hypocalcemia risk.

2 | MATERIALS AND METHODS

2.1 | Case selection and preoperative data

In this ambidirectional cohort study, the electronic medical records from a single academic institution were searched from June 13, 2007 to August 1, 2016 for canine patients with the diagnosis PHPT. In addition, dogs presenting to the hospital for surgical treatment of PHPT from August 2, 2016 to June 28, 2019 were eligible for enrollment in the prospective portion of this study. To meet inclusion criteria, dogs had to have a cervical ultrasound and a subsequent parathyroidectomy with resolution of their hypercalcemia following surgery. Dogs were excluded from the study if they failed to meet the previously mentioned criteria or there was uncertainty in the record regarding their ultrasonographic, surgical, or histopathological findings, or if such data was missing. Extracted data included information on signalment (age, sex, neuter status, weight, and breed), type and length of preoperative clinical signs, preoperative parathyroid hormone (PTH), calcium and phosphorus concentrations, length of documented hypercalcemia, and whether any preoperative medication was administered for calciuresis.

2.2 | Cervical ultrasound

All cervical ultrasounds were performed by a board certified veterinary radiologist or a diagnostic imaging resident under their direct supervision. Data from ultrasonographic records included: the number of parathyroid glands deemed to be abnormal by the performing radiologist, side of affected glands, and the maximum dimension of any affected glands using electronic calipers. Normal parathyroid glands measure ≤2 mm in length and this measurement was considered by the ultrasonographer when determining whether or not the gland was abnormal.[21] The side of the abnormal parathyroid gland was defined as being in either the left thyroid lobe, right thyroid lobe, or both lobes. If the location of the gland was remote to the thyroid lobe it was classified as ectopic.

2.3 | Surgical and histopathology findings

Bilateral cervical exploration and parathyroidectomies were performed by board certified veterinary surgeons or by a surgical resident under their direct supervision. Data extracted from surgical records included: the number of parathyroid glands deemed abnormal on cervical exploration and side of the affected parathyroid glands (left, right, or both), as described for the cervical ultrasounds. Histopathologic diagnosis of each of the surgically resected glands was recorded and grouped as adenoma, adenocarcinoma, hyperplasia, or other. Surgically removed tissue that was suspected to be parathyroid during intraoperative visual assessment but was not confirmed as such on histopathology, was also recorded.

2.4 | Definition of agreement between diagnostic modalities

Agreement between ultrasonographic and surgical findings on the number of glands affected was defined as the number of affected glands on cervical ultrasound being equal to the number deemed affected by the operating surgeon. Agreement in ultrasonographic and surgical findings between the side (left, right, or both) were recorded. Complete agreement between ultrasonographic and surgical findings was defined as agreement between both the side and number of glands affected. When all tissue removed at the time of surgery (that was thought to be pathologic by the operating surgeon) was classified as parathyroid adenoma, adenocarcinoma or hyperplasia on histopathology, agreement between surgical findings and histopathologic findings was met.

2.5 | Postoperative subclinical or clinical hypocalcemia

Records of clinical and laboratory outcomes included whether or not the animal became subclinically or clinically hypocalcemic postoperatively. Follow-up was obtained by review of the medical record or by referring veterinarian interview. Subclinical hypocalcemia was defined as a serum ionized calcium (iCa) concentration below the lower physiological range provided by the institution's clinical pathology laboratory (<1.18 mEq/L) with no associated clinical signs. Clinical hypocalcemia was defined as a serum iCa concentration below the lower physiological range with associated clinical signs. Signs of clinical hypocalcemia included tremors, weakness, pruritis, and seizures. Postoperative treatment with vitamin D and/or calcium supplementation was recorded along with the lowest serum calcium concentrations achieved. To account for the effect of prophylactic calcitriol and/or calcium supplementation on the development of clinical or subclinical hypocalcemia, animals were considered to have received prophylactic treatment if supplementation occurred before the event (development of subclinical or clinical hypercalcemia) and to have not received prophylactic treatment if supplementation occurred after the development of the event.

2.6 | Analytical approach

Data from this convenience sample were first extracted from the medical record system and organized according to study objectives. All statistical analyses were performed using commercially available statistical software (JMP v. 14.0.0, SAS Institute, Cary, North Carolina) except for multirater agreement statistics that were performed in R (R Core team 2017, Vienna, Austria). Results are reported as median (range) or mean ± SE unless otherwise specified in the text. Significance was set at $P < .05$. Difference from a hypothesized 1:1 male to female ratio of patients was analyzed using Pearson Chi-square.

2.6.1 | Ultrasonographic, surgical, and histopathological findings

Agreement statistics between the categorical variables recorded for ultrasound, surgery, and histopathology outcomes (number and side) were performed using Cohen's kappa statistic and associated 95% CI. Magnitude of agreement was interpreted following guidelines provided by Landis and Koch: 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1 almost perfect agreement.[23] Associations between prevailing histopathology diagnosis and the number of glands thought to be pathologic on cervical ultrasound or during intraoperative visual assessment was analyzed using Fisher's exact test. Differences in ultrasonographic lesion size by type of histopathologically confirmed lesion was analyzed using one-way ANOVA. A nominal logistic regression analysis was used to generate a receiver-operating characteristic (ROC) curve to determine the best size cut-off to differentiate carcinomas from adenomas and hyperplasia.

2.6.2 | Clinical outcome: Development of subclinical and clinical hypocalcemia

Univariable screening was performed to explore associations between the outcomes of subclinical or clinical hypocalcemia and all exposure variables of interest. Age and weight were considered as confounders and forced into all models. Variables with a univariable screening of $P < .20$ were offered to the initial multivariable logistic regression with manual backward stepwise elimination until all remaining variables in the multivariable reached a $P < .10$. Then, two separate models were built for the outcome of subclinical hypocalcemia, (1) including all animals, and (2) including only animals that did not receive prophylactic treatment for hypocalcemia. For the outcome of clinical hypocalcemia, only a model including all dogs was built due to the small number of dogs with the outcome of interest ($n = 4$) after all treated dogs were removed. Final model results were reported as adjusted odds ratios (aOR) with respective 95% CI.

Given the expected strong associations with preoperative serum iCa in the development of postoperative hypocalcemia, the population of dogs not receiving prophylactic treatment was also used to conduct a logistic regression with ROC analysis to explore the association of preoperative serum iCa concentration with the development of subclinical hypocalcemia. This analysis was used to define the cut-off of preoperative serum iCa concentration with the best discriminatory ability to correctly identify untreated animals that did or did not develop hypocalcemia after surgery.

3 | RESULTS

3.1 | Descriptive statistics

A total of 47 dogs were enrolled in this cohort study consisting of 34 retrospectively and 13 prospectively enrolled cases. The median age was 10 years (range, 4–14) and the median weight was 17.3 kg (range, 5–78). There were 14 (30.0%) spayed female and 33 (70%) male dogs. Neutered males were overrepresented in the enrolled study population ($P < .01$). The most prevalent breeds were mixed (14/47, 29.8%), Dachshund (6/47, 12.8%), shih-tzu (4/47, 8.5%), Staffordshire bull terriers (2/47, 4.3%) and keeshonds (2/47, 4.3%). There was 1 dog of each of the following breeds: Australian shepherd, basset hound, beagle hound, bichon frisé, blue tick coon hound, bull terrier, collie, English setter, German shepherd, golden retriever, great Dane, great Pyrenees, Pekingese, red bone hound, Rhodesian ridgeback, Siberian husky, Weimaraner, West Highland white terrier, and wire fox terrier.

Preoperative clinical signs included: polydipsia (25/47, 53.2%), polyuria (23/47, 48.9%), weakness (14/47, 29.8%), lethargy (12/47, 25.5%), general malaise (12/47, 25.5%), calcium oxalate urinary stones (9/47, 19.1%), tremors (6/47, 12.8%), vomiting (4/47, 8.5%), polyphagia (3/47, 6.4%), and diarrhea (2/47, 4.3%). Clinical signs were present a median of 2 months (range, 0–13) prior to cervical exploratory surgery. A total of 9 (19.1%) dogs were asymptomatic at the time of consultation.

The median length of documented hypercalcemia prior to surgery was 3 months (range, 0.5–28). The median preoperative serum iCa concentration was 1.78 mEq/L (range, 1.39–2.62), median parathyroid hormone concentration was 3.8 pmol/L (range, 1.0–49.5), and the median calcium phosphorous product was 34.3 (range, 22.7–60.0). Out of the 47 cases, 5 (10.6%) received medication preoperatively to decrease their serum calcium concentrations: 4 (8.5%) received furosemide and 1 (2.1%) received furosemide and prednisolone.

Postoperative medication was given for treatment or for prophylaxis of hypocalcemia in 26/47 (55.3%) of cases: 1 (3.8%) dog received calcium carbonate only, 9 (34.6%) received calcitriol only, and 16 (61.5%) received both calcium carbonate and calcitriol. The median time from surgery to the lowest measured calcium concentration in all dogs was 48 h (range, 3–158). Twenty-two (47%) of the forty-seven dogs developed hypocalcemia (iCa < 1.18 mEq/L) based on laboratory values following parathyroidectomy, with a median onset of 40 h (range 10–150). Eight of these twenty-two dogs (36%) developed clinical hypocalcemia with a median time to onset of 4 days (range 2–55). Clinical signs of hypocalcemia included: tremors (5/8, 62.5%), facial pruritis (3/8, 37.5%), inappetence (3/8, 37.5%), hypersalivation (1/8, 12.5%), weakness (1/8, 12.5%), polyuria/polydipsia (1/8, 12.5%), and seizures (1/8, 12.5%).

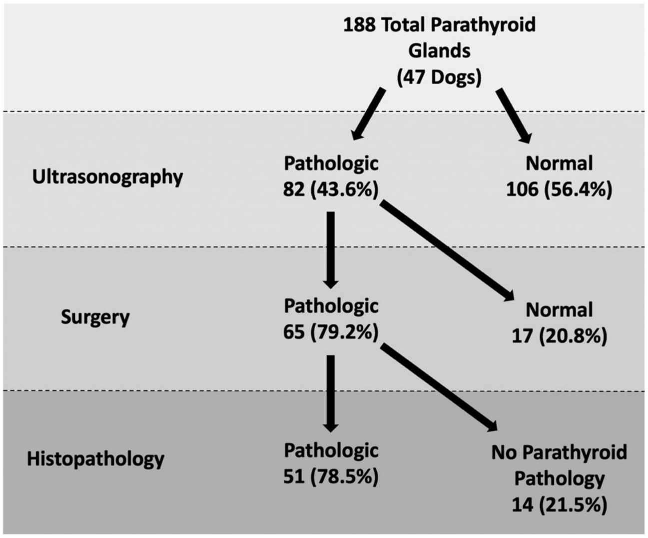

FIGURE 1 A flow diagram representing the ultrasonographic, intraoperative, and histopathologic categorization of pathologic versus normal parathyroid glands examined in 47 dogs undergoing parathyroidectomy for primary hyperparathyroidism

3.2 | Ultrasonographic, surgical, and histopathologic findings

Ultrasonographic, surgical, and histopathologic findings are summarized in Figure 1. A total of 188 parathyroid glands were examined by ultrasonography and 82 were classified as pathologic. The median of the maximum dimension of all pathologic glands on ultrasound was 6 mm (range, 2–16). On ultrasound examination 24/47 (51%) dogs had one gland affected, 15 (32%) had 2 glands affected, 4 (8.5%) had 3 glands affected, and 4 (8.5%) had 4 glands affected. Among the 47 dogs, 14 (30%) had left sided disease, 15 (31.9%) had right sided disease, and 18 (38.3%) had bilateral disease on ultrasonographic examination. Ectopic parathyroid tissue was not identified on ultrasound or at surgery for any of the dogs included in this study.

Of the 82 glands thought to be pathologic on ultrasonographic examination, 65 (79.2%) were deemed to be so with direct intraoperative observation. Of the 47 dogs that underwent surgery, 18 (38.3%) had left sided disease, 19 (40.4%) had right sided disease, and 10 (21.3%) had bilateral disease. One gland was removed in 33 (70%) cases, 2 glands were removed in 10 (21%) cases and 4 dogs (9%) had 3 glands removed.

Of the 65 glands excised at surgery, 51 (78.5%) were found to be parathyroid tissue and to have pathology consistent with a cause of PHPT. Histopathologic diagnosis for those 51 glands included 33 (64.7%) adenomas, 11 (21.6%) hyperplastic parathyroid glands, and 7 (13.7%) carcinomas. The histopathologic findings for the remaining 14 removed nodules were: thyroid cyst (3), mineralization of thyroid follicles (1), diffuse thyroid C cell hyperplasia (1), ultimobranchial cyst (1), thyroglossal duct cyst (1), parafollicular cell hyperplasia (1), incidental parathyroid cysts (1), multifocal thyroid cystadenoma (1), or normal parathyroid tissue (4). In 11/47 (23.4%) dogs, superfluous tissue was removed by the surgeon that was not consistent with a cause for PHPT.

3.3 | Agreement statistics

Agreement between ultrasonography and surgery in the number of glands (1–4) affected was fair (31/47 cases, 65.9%, $\kappa = 0.40$ [0.21 to 0.59]), and substantial (34/47 cases, 72.3%, $\kappa = 0.59$ [0.40 to 0.78]) for the side of the glands (left, right, and bilateral). Both the side and number of glands affected was consistent between modalities in 30/47 (63.8%) cases. Agreement of histopathology and surgery on the number of glands affected was moderate (37/47 cases, 78.7%, $\kappa = 0.46$ [0.22 to 0.70]). In 23/47 (48.9%) of cases, the number of affected parathyroid glands was consistent between ultrasonography, surgery and histopathology (fair agreement, $\kappa = 0.33$ [0.20 to 0.45]).

3.4 | Associations with parathyroid morphology and diagnosis

Maximal ultrasonographic dimension was compared with the histologic diagnoses which revealed that the median maximal dimension of hyperplastic parathyroid glands [4.0 mm (range, 2.0–8.1); n = 11] and adenomas [5.0 mm (range, 4.0–9.0); n = 33], was smaller than carcinomas [8.4 mm (4.0–16.0); n = 7] ($P < .001$), whereas there was no difference between hyperplastic glands and adenomas ($P = .33$). A receiver operating characteristic curve showed a high AUC of 0.82, and the best cut-off to differentiate carcinomas from both adenomas and hyperplasia was ≥8.0 mm, at which 5/7 (71.4%) of carcinomas and 39/44 (88.6%) of adenomas or hyperplasia were correctly identified based on maximum ultrasonographic dimension alone.

There was no association found between the number of glands seen affected on ultrasonographic examination and the prevailing diagnosis on histopathology (Fisher's exact test $P \leq .26$), or between the number of glands deemed to be affected by the operating surgeon and the prevailing diagnosis on histopathology (Fisher's exact test $P = .57$).

3.5 | Administration of prophylactic medication for hypocalcemia

Administration of calcitriol and/or calcium carbonate was initiated immediately after surgery and prior to the development of subclinical or clinical hypocalcemia in

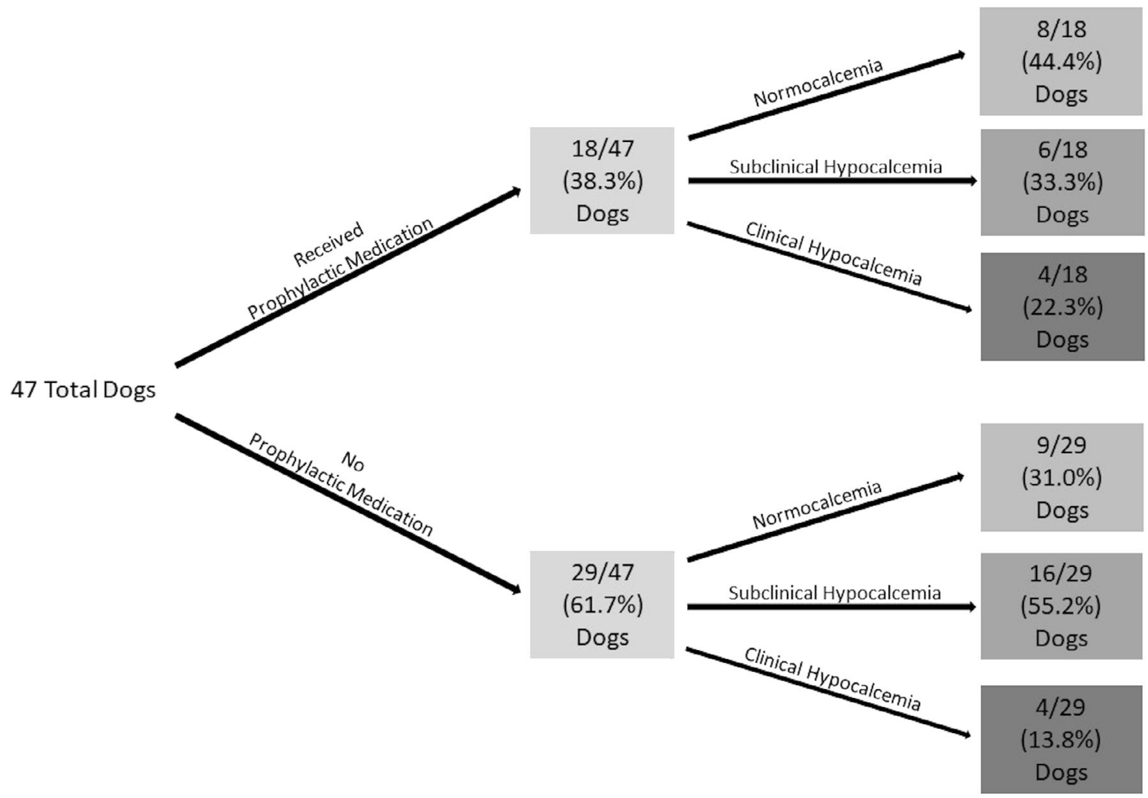

FIGURE 2 A schematic illustrating the postoperative outcome (normocalcemia, subclinical hypocalcemia, or clinical hypocalcemia) for all 47 dogs in relation to whether or not they received prophylactic medication (calcitriol or calcium carbonate immediately after cervical exploratory surgery and before the onset of hypocalcemia)

18/47 (38.3%) of cases at the discretion of the treating veterinarian (Figure 2). There was no significant difference in studied variables between those dogs that received prophylactic medication for hypocalcemia and those that did not. Of the 22 dogs that developed subclinical hypocalcemia, 6/22 (27%) were treated prophylactically, 8/22 (34.6%) were treated after the diagnosis of subclinical hypocalcemia had been made, and 8/22 (34.6%) were not treated for hypocalcemia at any time point. Of the 8 dogs that developed clinical hypocalcemia, 4/8 (50.0%) had received prophylactic supplementation and 4/8 (50.0%) had not. The 4 dogs that did not receive prophylactic treatment and developed clinical hypocalcemia received treatment after the development of clinical signs. No association was found with the administration of prophylactic medication and the development of postoperative hypocalcemia ($P = .37$).

3.6 | Associations with development of subclinical or clinical hypocalcemia

3.6.1 | Subclinical hypocalcemia (22 dogs)

Twenty-two (46.8%) dogs developed subclinical hypocalcemia. No associations were found between the development of subclinical hypocalcemia and histopathologic diagnosis.

When considering all dogs (those that did, and those that did not receive prophylactic medication for hypocalcemia), every 0.1 mEq/L increase in preoperative iCa concentration increased the odds of development of subclinical hypocalcemia postoperatively by 1.26 times (aOR 1.26 [1.00 to 1.61]; $P = .04$).

When only considering dogs that did not receive prophylactic treatment for hypocalcemia ($n = 29$) this relationship was still present, and for every 0.1 mEq/L increase in preoperative iCa concentration there was a 1.39 (0.96 to 2.00) greater adjusted odds of developing subclinical hypocalcemia ($P = .04$).

3.6.2 | Clinical hypocalcemia (8 dogs)

Eight (17.0%) dogs developed clinical hypocalcemia. For every 0.1 mEq/L increase in iCa concentration preoperatively, adjusted odds were 1.48 (1.12 to 1.94) times greater to develop clinical hypocalcemia ($P = .01$).

No intent was made to build a model for dogs that did not receive prophylactic medication due to the small number of dogs remaining ($n = 4$). No associations were found between any other variable and the development of clinical hypocalcemia.

3.6.3 | Association of preoperative serum iCa concentration and postoperative hypocalcemia

The ROC analysis revealed a moderately high AUC of 0.74 and a cut-off of ≥1.75 mEq/L that correctly identified 11/16 (68.8%) animals that developed hypocalcemia, and 10/13 (76.9%) that did not develop hypocalcemia among the 29 untreated dogs. The odds of becoming subclinically hypocalcemic were 7.50 (1.16 to 48.45) times greater for dogs that had a preoperative iCa concentration of ≥1.75 mEq/L (13/29) than those that did not.

This association approached significance within the clinical hypocalcemic group but the low numbers precluded accurate analysis.

4 | DISCUSSION

This study found a moderate agreement between ultrasonography and surgery when considering the side of the parathyroid pathology (72.3%, $\kappa = 0.59$), and fair agreement when considering the number of glands affected (65.9%, $\kappa = 0.40$). Our findings are consistent with previous reports that described discrepancies between the side of the lesion on ultrasonographic examination and at surgery at 19%.[11] This inconsistency in identifying parathyroid pathology on ultrasonographic examination may explain the previous reports of inferior cure rates of ultrasound guided parathyroid gland ablation when compared with surgical excision; approximately 70% versus 95%, respectively.[10–12,14] In addition, this finding provides continued support for bilateral exploration during parathyroidectomy for identification of abnormal parathyroid glands for treatment of PHPT.[10,14,15]

Although surgeons were found to be more successful at identifying parathyroid pathology, at least 23.4% of all dogs that went to surgery for a PHPT had at least some tissue removed that was not pathologic parathyroid gland. This overestimation and inability to correctly identify pathologic parathyroid glands does not seem to affect the success rates of parathyroidectomy in the treatment of PHPT, however, this may prove to be a limitation in the development of minimally invasive techniques. In human medicine, parathyroidectomies are predominantly performed using minimally invasive video-assisted procedures which focus on only visualizing and approaching the suspected affected gland.[10,24] With this procedure an emphasis is placed on unequivocally localizing the cause of PHPT preoperatively using more accurate diagnostic techniques in comparison to veterinary medicine.[10,24,25] These include nuclear medicine scintigraphy and 4-dimensional CT in concert with intraoperative real-time PTH monitoring to minimize unnecessary surgical resection.[25] Results of a human study suggest that with this thorough pre and intraoperative diagnostic approach 1030/1037 (99.4%) patients achieved a normalization of both serum PTH and calcium.[24] Although real time PTH monitoring has been described in dogs, it is not widely available in practice at this time.[18] In addition, nuclear scintigraphy has been evaluated in a single study for use in dogs and so far has been unsuccessful at correctly identifying parathyroid pathology.[26] Additional research within veterinary medicine is warranted to determine if a similar diagnostic approach, as used in humans, could improve the identification and removal of pathologic parathyroid tissue in dogs while remaining cost effective.

In agreement with our hypothesis, carcinomas were found to be consistently larger than parathyroid adenomas and hyperplastic parathyroid glands allowing us to establish a robust cut-off value of ≥8.0 mm for a parathyroid carcinoma. In this study, 88.6% of benign pathologies were identified based on this cut-off value. There was no association with the number of glands thought to be pathologic on ultrasonography or during intraoperative visual assessment and prevailing histopathologic diagnosis. Previous studies have reported that hyperplastic parathyroid glands measure <4.0 mm and neoplastic glands (adenomas and carcinomas) measure >4.0 mm.[3,21] Further studies have sought to establish a reliable differentiation in size between adenomas (~4.0–6.0 mm in size) and carcinomas (~7.0 mm).[9,14] While there remains some significant overlap in ultrasonographic size and pathology, a differential diagnosis of carcinoma should be considered for large parathyroid nodules.[3,9,14,21] Parathyroid carcinoma is a rare disease, with limited data indicating a low rate of metastasis and median survival time of 2 years.[14,19,20] The cases in this study with carcinoma were not followed to assess for the development of metastasis. However, considering the lack of research and the risk of carcinoma metastasis in general, the authors would encourage greater urgency to operate on these cases rather than taking a conservative approach.[27] In addition, a parathyroidectomy rather than ultrasound guided minimally invasive techniques for treatment of large parathyroid nodules may be prudent.

The most commonly encountered complication following parathyroid ablation or parathyroidectomy is development of postoperative hypocalcemia.[2,4–6,11,15] Clinical hypocalcemia can be challenging to treat and may be refractory to medical management.[6,11,13] An ability to predict which dogs will become hypocalcemic following parathyroidectomy or parathyroid ablation for PHPT remains elusive.[4,6,7,15] In this study, 47% of cases became subclinically hypocalcemic and 17% became clinically hypocalcemic postoperatively which is consistent with previous reports in the literature.[8,9,11] We could find no associations with the chronicity of preoperative hypercalcemia and becoming hypocalcemic following parathyroidectomy, refuting the findings of a previous report.[6] Additionally, no associations were found between histopathologic diagnosis and the development of subclinical or clinical hypocalcemia.

An association was found in this study with a preoperative iCa ≥1.75 mEq/L and the development of postoperative hypocalcemia. A tCa of 14.0 mEq/L, which is approximately equivalent to an iCa of 1.75 mEq/L assuming comparable concentrations of each calcium-ligand complex, had been previously identified as a cut-off for the development of hypocalcemia in dogs post-parathyroidectomy.[1,28] However, several studies within the last decade have refuted this hypothesis and have instead asserted that preoperative iCa is not predictive of postoperative hypocalcemia in dogs undergoing parathyroidectomy for PHPT.[4,6,11,15] In contrast to these reports, our study showed elevated preoperative iCa as a positive predictive indicator of developing postoperative hypocalcemia. The association with iCa remained when considering only those dogs that did not receive any prophylactic management of postoperative hypocalcemia. Removal of the potential confounding effect of prophylactic treatment was not performed in previous studies that did not find an association with high iCa and postoperative hypercalcemia.[4,15] While our findings do not endorse a strict cut-off of an iCa ≥1.75 mEq/L, they do support that these patients are at a statistically significant greater risk for developing hypocalcemia postoperatively and should be diligently monitored.

For all 47 cases the median time to the lowest calcium value was 48 h. In addition, the 8 dogs that developed clinical hypocalcemia did not do so until a median of 4 days postoperatively (range 2–55 days). One dog in our group presented with clinical signs of hypocalcemia (muscular tremors with an ionized calcium of 0.8 mEq/L) at 55 days post-surgery following cessation of vitamin D and calcium supplementation around this time. Clinicians should be mindful of these timeframes when monitoring serum calcium levels postoperatively and actively include them in their decision making regarding the amount of hospitalization time for patients. Clients should be dutifully educated about risk and clinical signs of hypocalcemia should their dog develop clinical hypocalcemia following discharge from the hospital and require re-admittance.

There was no association between developing clinical hypocalcemia and receiving prophylactic calcitriol or calcium supplementation in this study even in the face of elevated preoperative serum iCa concentration. Evidence on the utility of administering prophylactic medication to prevent postoperative hypocalcemia is conflicted.[4,6,15] Prophylactic treatment for dogs with severe preoperative hypercalcemia was considered warranted in one study, while it was determined to not be beneficial in two others.[4,6,15] Prophylactic supplementation is frequently used in the belief that it provides the body time to adjust and to achieve calcium homeostasis following the abrupt reduction in pathologically elevated PTH levels, thereby providing a protective effect against hypocalcemia in the immediate postoperative setting.[15] Arguments for not using prophylactic treatment include elimination of potential suppression of the non-pathologic parathyroid glands and a reduction in client expense. Supplementation type, dose, and frequency was not standardized in this study and was left to clinician preference. The inconsistency between manuscripts regarding the administration of prophylactic medication highlights the inherent inefficiencies of retrospective studies and a prospective randomized study is warranted to provide better clarification to this perioperative therapeutic dilema.[4,6,15]

There were several limitations to this study. Given the time-frame over which data was collected, diagnostic accuracy may have been influenced by advancements in imaging technology. Several different American College of Veterinary-boarded radiologists, surgeons, and pathologists participated in the diagnosis and treatment of the dogs. Thus, there may have been a level of subjective variability in the assessment of the parathyroid glands in each case. In addition, 33 of the 47 (70.2%) cases included in this study were examined retrospectively which inherently leads to case selection bias and deficiency in records. The number of cases included in this study was small, which is reflective of the low incidence of primary hyperparathyroidism in the clinical population. An inherent bias also exists in this study as each diagnostic modality was dependent on another to determine its accuracy. All dogs had resolution of their hypercalcemia postoperatively so the assumption was made that surgeons were successful in identifying and removing pathologic parathyroid tissue. However, all glands determined to be pathologic on ultrasonographic examination were not sent to histopathology, and there is an assumption that the surgeon removed only tissue that they assessed as pathologic parathyroid tissue. As ethics preclude the ability to remove and submit all four parathyroid glands for histopathology in an observational study on dogs with naturally occurring PHPT, the true accuracy of ultrasonography and direct intraoperative assessment may never be known. The assessment of parathyroid pathology and underlying discrepancies between surgical, ultrasonographic, and histopathologic findings, however, still hold clinical relevance.

In conclusion, ultrasonography is only a moderately reliable tool in evaluating parathyroid pathology, indicating the importance of bilateral parathyroid surgical exploration in dogs with PHPT. A preoperative serum iCa concentration ≥1.75 mEq/L, had a significant association with postoperative hypocalcemia in dogs undergoing surgical treatment for PHPT. These dogs should be closely monitored postoperatively considering their increased risk of developing hypocalcemia. No other variables were found in this study to be associated with to the development of postoperative hypocalcemia including prophylactic treatment and the length of preoperative hypocalcemia. Parathyroid carcinomas are more likely to measure ≥8 mm on ultrasonographic examination; considering the malignancy of this pathology the authors would encourage their surgical removal. Prospective studies are encouraged to evaluate other diagnostic alternatives to improve the accuracy of identification of pathologic parathyroid glands.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this report.

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