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Predicting outcomes in hyperthyroid cats treated with radioiodine

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Abstract

Background: Radioiodine (^{131}I) is the treatment of choice for cats with hyperthyroidism. After ^{131}I, however, euthyroidism is not always achieved, with 5% to 10% of cats remaining persistently hyperthyroid and 20% to 50% developing iatrogenic hypothyroidism.

Objectives: To identify pretreatment factors that may help predict persistent hyperthyroidism and iatrogenic hypothyroidism after treatment of cats using a novel ^{131}I dosing algorithm.

Animals: One thousand and four hundred hyperthyroid cats treated with ^{131}I.

Methods: Prospective, before-and-after study. Pretreatment predictors (clinical, laboratory, scintigraphic, ^{131}I dose, ^{131}I uptake measurements) of treatment failure or iatrogenic hypothyroidism were identified by multivariable logistic regression analysis.

Results: Cats that developed iatrogenic hypothyroidism were more likely to be older (odds ratio [OR] = 1.10; 95% confidence interval [CI], 1.04-1.17; $P = .001$), female (OR = 2.04; 95% CI, 1.54-2.70; $P < .001$), have detectable serum thyroid-stimulating hormone (TSH) concentrations (OR = 4.19; 95% CI, 2.0-8.81; $P < .001$), have bilateral thyroid nodules (OR = 1.57; 95% CI, 1.19-2.08; $P < .001$), have homogeneous, bilateral distribution of ^{99m}Tc-pertechnetate uptake (OR = 2.93; 95% CI, 2.05-4.19; $P < .001$), have milder severity score (OR = 0.62; 95% CI, 0.49-0.79; $P < .001$), and have higher ^{131}I uptake (OR = 2.40; 95% CI, 1.75-3.28; $P < .001$). In contrast, cats remaining persistently hyperthyroid were more likely to be younger (OR = 0.81; 95% CI, 0.72-0.92; $P < .001$), have higher severity score (OR = 1.87; 95% CI, 1.51-2.31; $P < .001$), and have lower ^{131}I uptake (OR = 3.50; 95% CI, 1.8-6.80; $P < .001$).

Conclusions and Clinical Importance: Age, sex, serum TSH concentration, bilateral and homogeneous ^{99m}Tc-pertechnetate uptake on scintigraphy, severity score, and percent ^{131}I uptake are all factors that might help predict outcome of ^{131}I treatment in hyperthyroid cats. Cats with persistent hyperthyroidism had many predictive factors that directly contrasted those of cats that developed ^{131}I-induced hypothyroidism.

Abbreviations: ^{131}I, radioiodine; CI, confidence interval; IQR, interquartile range; mCi, millicurie; OR, odds ratio; T_3, triiodothyronine; T_4, thyroxine; TcTU, percent thyroidal uptake of sodium ^{99m}Tc-pertechnetate; TSH, thyroid-stimulating hormone.

KEYWORDS
^{131}I, feline, hypothyroidism, radioactive iodine, thyroid gland, treatment failure

1 | INTRODUCTION

Radioiodine (^{131}I) is considered the treatment of choice for hyperthyroidism in cats. Although the goal of ^{131}I treatment is to restore euthyroidism with a single dose of radiation without producing hypothyroidism, most current dosing protocols fail to achieve this goal in all cats, with 30% to 50% of ^{131}I-treated cats developing iatrogenic hypothyroidism after treatment.[1-5] Conversely, 5% to 10% of hyperthyroid cats fail ^{131}I treatment and remain persistently hyperthyroid, requiring retreatment with ^{131}I or alternative treatment with methimazole or surgical thyroidectomy.[1-6] The optimal ^{131}I dose that will both maximize the chance of curing hyperthyroidism but minimize the risk of developing hypothyroidism is highly variable among individual cats and, therefore, is difficult to calculate. We recently published the results of a large cohort of hyperthyroid cats treated with individualized ^{131}I doses using a novel algorithm, calculated to administer the lowest effective dose possible.[7] With this dosing algorithm, we achieved euthyroidism at rates similar to previous studies using conventional dosing protocols (>95%), despite much lower ^{131}I doses, without increasing the probability of treatment failure (persistent hyperthyroidism). With this approach, the prevalence of overt hypothyroidism fell below 5%, but nearly 20% of ^{131}I-treated cats still developed mild (subclinical) hypothyroidism.[7] Therefore, the outcome of ^{131}I treatment remains difficult to predict with certainty and is far from perfect. Identifying factors that predict undesired outcomes could allow clinicians to modify treatment protocols and improve treatment outcomes.

Consequently, we sought to identify pretreatment factors that might help better predict the outcome of ^{131}I treatment when using our algorithm, specifically, which cats will develop iatrogenic hypothyroidism or fail ^{131}I treatment and remain persistently hyperthyroid.

2 | MATERIALS AND METHODS

2.1 | Study population

The clinical details of the 1400 hyperthyroid cats in our study have been previously reported.[7] To be eligible for inclusion, cats underwent an evaluation that included a complete physical examination, routine

TABLE 1 Pretreatment signalment data and serum thyroid and creatinine concentrations in 1400 ^{131}I-treated cats, divided into in 4 thyroid outcome groups

Variable	All cats (1400)	Euthyroid (1047)	Overt hypothyroid (57)	Subclinical hypothyroid (240)	Persistent hyperthyroid (56)	*P* value
Age (years)	12 (10-14)	12^{abc} (10-14)	13^{ad} (12-15)	13^{be} (11-14)	10.5^{cde} (9-13)	<.001*
Breed (mixed : pure breed ratio)	1255:125 (8.6)	930:117 (8.0)	52:5 (10.4)	222:18 (12.3)	51:5 (10.2)	.37†
Sex (female : male ratio)	751:649 (1.16)	522:535 (0.98)^{ab}	41:16 (2.56)^{a}	157:83 (1.90)^{b}	31:25 (1.24)	<.001†
Body weight (kg)	4.4 (3.7-5.3)	4.5^{a} (3.7-5.3)	4.1 (3.2-4.9)	4.2^{a} (3.4-5.1)	4.4 (3.7-5.3)	.008*
Underweight	376 (26.9%)	263 (25.1%)	17 (29.8)	75 (31.1%)	20 (35.7%)	.08†
Overweight	198 (14.1%)	151 (14.4%)	10 (17.5%)	36 (15.0%)	9 (16.1%)	.9†
Time from diagnosis (days)	65 (31-197)	64 (31-190)	89 (44-220)	60 (32-199)	77.5 (29-288)	.21*
Prior treatment with methimazole	728 (52%)	520 (49.7%)	37 (64.9%)	136 (56.7%)	35 (62.5%)	.02†
Serum T_4 (μg/dL)	8.9 (6.5-11.9)	8.9^{ab} (6.6-11.9)	7.9^{c} (5.8-10.8)	8.0^{a,d} (5.9-10.8)	15.0^{b,c,d} (11.1-21.6)	<.001*
Serum T_3 (ng/dL)	133 (88-211)	134^{a} (88-210)	110^{b} (75-152)	111^{c} (84-178)	278^{a,b,c} (190-429)	<.001*
Serum TSH (ng/mL)	0.02 (0.02-0.02)	0.02^{a} (0.02-0.02)	0.02^{a,b,c} (0.02-0.03)	0.02^{b} (0.02-0.02)	0.02^{c} (0.02-0.02)	<.001*
Detectable TSH concentration	34 (2.4%)	16^{a,b} (1.5%)	8^{a,c} (14.0%)	10^{b} (4.2%)	0^{c} (0)	<.001†

Note: All continuous data (age, body weight, time from diagnosis, serum T4, TSH, and creatinine) are expressed as median (25th-75th percentile). All qualitative data are expressed as ratio (breed, sex) or number (%) of cats (underweight, overweight, detectable TSH concentration). Reference intervals: T_4 = 1.0 to 3.8 μg/d; T_3 = 30 to 80 ng/dL; TSH = <0.03 to 0.3 ng/mL. Values with the same superscript letters are significantly different to one another.
Abbreviation: TSH, thyroid-stimulating hormone.
*Kruskal-Wallis test, followed by Dunn multiple comparisons test.
†Chi-square test, followed by the Holm-Bonferroni correction procedure for within group comparison.

TABLE 2 Thyroid scintigraphy variables and measurements in 1400 ^{131}I-treated cats, divided into in 4 thyroid outcome groups

Variable	All cats (1400)	Euthyroid (1047)	Overt hypothyroid (57)	Subclinical hypothyroid (240)	Persistent hyperthyroid (56)	*P* value
Bilateral : unilateral nodule	753:647 (1.16)	531:516 (1.03)^{a,b,c}	40:17 (2.35)^{a}	144:96 (1.50)^{b}	38:18 (2.1)^{c}	<.001†
Heterogeneous : homogeneous bilateral uptake	568:185 (3.07)	426:105 (4.06)^{a,b}	23:17 (1.35)^{a}	88:56 (1.57)^{b}	31:7 (4.43)	<.001†
Thyroid : salivary ratio	5.3 (3.2-9.0)	5.2^{a} (3.1-8.8)	5.4^{b} (3.0-8.3)	5.0^{c} (3.4-8.5)	8.1^{a,b,c} (5.1-14.8)	<.001*
Thyroid : axillary ratio	16.6 (10-29.7)	16.5^{a} (10-29.4)	16.5^{b} (8.9-30.8)	15.3^{c} (9.7-27.3)	27.6^{a,b,c} (16.6-43.6)	<.001*
Thyroid : tracheal ratio	11.0 (6.7-18.2)	11.1^{a} (6.9-18.5)	11.6 (6.2-20.2)	9.4^{b} (6.4-16.4)	14.6^{a,b} (10.8-21.8)	.002*
Thyroid : heart ratio	5.4 (3.2-9.5)	5.4^{a} (3.2-9.6)	5.7 (3.3-9.3)	4.9^{b} (3.2-8.2)	8.7^{a,b} (5.2-12.2)	<.001*
Percent thyroidal uptake of ^{99m}Tc-pertechnetate (TcTU)	3.2^{a} (1.9-5.8)	3.1^{a} (1.8-5.7)	2.9^{b} (2.1-6.2)	3.1^{c} (1.9-5.6)	6.5^{a,b,c} (3.4-11.4)	<.001*
Thyroid volume (cm^3)	1.86 (1.5-2.3)	1.85^{a} (1.5-2.3)	1.80^{b} (1.6-2.2)	1.85^{c} (1.5-2.2)	2.30^{a,b,c} (1.9-3.3)	<.001*

Note: Qualitative data are expressed as ratio (unilateral : bilateral thyroid nodules; asymmetric : symmetric bilateral uptake pattern). Continuous data (T/S, T/A, T/T, T/H, TcTU, and volume) expressed as median (25th-75th percentile). Reference intervals: Thyroid : salivary ratio = 0.5 to 1.5; Thyroid : axillary ratio = 1.5 to 5.5; Thyroid : tracheal ratio = 1.5 to 3.5; Thyroid : heart ratio = 0.5 to 1.5; Percent thyroidal uptake of ^{99m}Tc-pertechnetate (TcTU) = 0.05 to 0.8; Thyroid volume = 0.2 to 1.0 cm^3. Values with the same superscript letters are significantly different to one another.

*Kruskal-Wallis test, followed by Dunn multiple comparisons test.

†Chi-square test, followed by the Holm-Bonferroni correction procedure for within group comparison.

laboratory testing (CBC, serum biochemical profile, complete urinalysis), determination of serum thyroid hormone concentrations (total thyroxine [T_4], triiodothyronine [T_3], and thyroid-stimulating hormone [TSH]),[2,8,9] and qualitative and quantitative thyroid scintigraphy.[10,11] In the 728 cats treated with methimazole, owners discontinued administration of the drug ≥1 week (median, 7 days; interquartile range [IQR], 7-15 days) before evaluation and treatment with ^{131}I.[7] Owners feeding a low-iodine diet (Hill's Prescription Diet y/d Feline, Topeka, Kansas) were instructed to feed an iodine-replete diet for at least 4 weeks before treatment. We excluded cats with pre-existing azotemia (defined as serum creatinine concentration > 2.0 mg/dL), as well as cats with multifocal thyroid disease (≥3 separate tumor nodules or areas of increased radionuclide uptake), a scintigraphic pattern that indicates a higher probability of thyroid carcinoma.[12,13]

The full details of the ^{131}I dosing algorithm used to treat the 1400 cats in our study have been previously reported.[7] In brief, we calculated individual ^{131}I doses for all cats, based on pretreatment serum T_4 and T_3 concentrations, estimated thyroid volume (measured from scintigraphic image), and the percent uptake of ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$). These variables contributed to a severity score, from which we calculated the ^{131}I dose. On day 1, we administered 80% of this calculated dose. Twenty-four hours later, we measured the percent ^{131}I uptake by the thyroid gland, and administered additional ^{131}I (as needed) to provide sufficient ^{131}I to meet the final calculated dose (based on the algorithm).

Based on the serum concentrations of T_4 and TSH at 6 to 12 months (median, 6 months) after ^{131}I treatment,[7] we classified thyroid status into 1 of 4 thyroid categories: euthyroid (T_4 = 1.0-3.8 μg/dL; TSH ≤0.30 ng/mL), overtly hypothyroid (T_4 < 1.0 μg/dL; TSH >0.30 ng/mL), subclinically hypothyroid (T_4 = 1.0-3.8 μg/dL; TSH >0.30 ng/mL), and persistently hyperthyroid (T_4 ≥ 3.9 μg/dL; TSH <0.03 ng/mL), as previously defined.[2,14,15]

2.2 | Data and statistical analyses

We first evaluated a large number of variables (listed in Tables 1-3) to determine which variables differed between outcome groups. For these analyses, we compared continuous variables between groups with Kruskal-Wallis tests, followed by Dunn's multiple comparisons test.[16,17] We compared categorical variables among groups using the chi-squared test or Fisher's exact test, where appropriate, followed by the Holm-Bonferroni correction procedure for within group comparisons.[18,19] We then selected variables that differed among outcome groups for initial inclusion in the explanatory model for regression analysis.

Using those selected variables, we then performed multivariable logistic regression analysis to further evaluate for factors that predicted the outcome of ^{131}I treatment.[20,21] In this analysis, we classified the outcome variable as being either persistent hyperthyroidism or iatrogenic hypothyroidism (unwanted outcomes) vs euthyroidism (ideal outcome). The hypothyroid cats also were subdivided into overt and subclinical subgroups and again compared to the euthyroid group. The following variables initially were evaluated as predictors of unwanted outcome: age; sex; serum, T_4, T_3, and TSH concentrations;

TABLE 3 Dosing score variables, 24-hour percent ^{131}I uptake, and final calculated ^{131}I dose in 1400 hyperthyroid cats, divided into 4 outcome groups

Variable	All cats (1400)	Euthyroid (1047)	Overt hypothyroid (57)	Subclinical hypothyroid (240)	Persistent hyperthyroid (56)	*P* value
Serum T4 and T3 score (mCi)	1.8 (1.7-2.2)	1.8[a] (1.7-2.2)	1.7[b] (1.7-1.9)	1.8[c] (1.7-2.1)	2.85[a,b,c] (2.0-2.9)	<.001*
TcTU score (mCi)	1.9 (1.7-2.2)	1.8[a] (1.7-2.2)	1.9[b] (1.7-2.2)	1.85[c] 1.7-2.2)	2.2[a,b,c] (1.9-3.3)	<.001*
Volume score (mCi)	1.86 (1.5-2.3)	1.85[a] (1.5-2.3)	1.8[b] (1.6-2.2)	1.85[c] (1.6-2.2)	2.3[a,b,c] (1.9-3.3)	<.001*
Overall score (mCi)	1.87 (1.7-2.3)	1.85[a] (1.7-2.1)	1.8[b] (1.6-2.1)	1.83[c] (1.7-2.1)	2.64[a,b,c] (2.0-3.5)	<.001*
^{131}I uptake (%)	22.0 (17.3-27.3)	21.5[a,b] (17-26.7)	27[a,c,d] (23.5-33)	23.4[b,c,e] (18.3-30)	19.4[d,e] (13.7-24.5)	<.001*
Final calculated dose (mCi)	1.87 (1.7-2.2)	1.88[a,b,c] (1.7-2.2)	1.68[a,d] (1.5-1.9)	1.81[b,e] (1.6-2.0)	2.72[c,d,e] (2.2-3.6)	<.001*

Note: Data expressed as median (25th-75th percentile). Values with the same superscript letters are significantly different to one another.
Abbreviation: TcTU, percent thyroidal uptake of sodium ^{99m}Tc-pertechnetate.
*Kruskal-Wallis test, followed by Dunn multiple comparisons test.

scintigraphic pattern of thyroid disease (unilateral vs bilateral nodules),[10] homogeneous vs heterogeneous distribution of $^{99m}TcO_4^-$ uptake in cats with bilateral disease (eg, cats with homogeneous uptake had an equivalent count density or thyroid-to-salivary ratio in both thyroid lobes, whereas those with heterogeneous distribution had dissimilar count densities in the 2 lobes);[10] thyroid-to-salivary ratio, percent thyroid uptake of $^{99m}TcO_4^-$ (TcTU), and thyroid tumor volume;[10,11] composite ^{131}I dose or severity score (ie, average of the thyroid hormone, thyroid volume, and TcTU scores); and percent ^{131}I thyroid uptake (low vs high uptake). The significance of each explanatory variable was tested using the Wald test. Biologically plausible, multiplicative 2-way interactions between the remaining variables were assessed for significance. We also examined the explanatory variables for multicollinearity[22,23] by calculating the coefficient of determination with other variables, as well as the variance inflation factor.[22,24] Because we identified a number of highly correlated variables among the ^{131}I dosing scores, we excluded the redundant variables (eg, serum T_4 and T_3 concentrations, thyroid hormone scores, volume scores, thyroid-to-salivary ratio, TcTU scores) and only used the composite ^{131}I dose score as the severity covariable. A regression coefficient was obtained for each individual variable, which was then used to estimate the odds ratio (OR) and calculate the 95% confidence interval (CI). The ORs represent the factor by which the probability of hypothyroidism or persistent hyperthyroidism is multiplied for the patients in the presence of the variable. To evaluate the model's abilities to discriminate between groups, we calculated the area under the receiver operating characteristic curve.[24]

For further analyses, the untreated hyperthyroid cats were categorized into 3 groups of disease severity (mild, moderate, and severe) based on their composite ^{131}I dose or severity score (ie, average of thyroid hormone score, TcTU score, and thyroid volume score). Cats with individual dose scores <1.8 mCi were grouped as having mild disease, those with dose scores 1.8 to 2.5 mCi as moderate disease, and cats with scores >2.5 mCi as severe disease. The selection of these cutoffs for disease severity was based on the cats' clinical signs and physical examination findings. For example, cats with mild disease generally had very small palpable thyroid nodule(s), only mild weight loss or muscle wasting, and normal heart rates. Cats with severe disease (dose or severity scores >2.5 mCi) tended to have large palpable thyroid nodules, moderate to severe weight loss and muscle wasting, and tachycardia. Cats with moderate disease had clinical features that were intermediate to the mild and severe cases. Similarly, the cats were categorized into 3 groups based on their percent ^{131}I thyroidal uptake. Cats with ^{131}I uptake <16% were classified as having low uptake, those with ^{131}I uptake between 16% and 28% as moderate uptake, and those with ^{131}I uptake >28% as having high uptake of ^{131}I. Again, the selection of cutoffs for low, mid, and high ^{131}I uptake was somewhat arbitrary and was not based on the result of any modeling.

For all analyses, statistical significance was defined as $P \leq .05$. All statistical analyses were performed using proprietary statistical software (GraphPad Prism, version 9.0; GraphPad Software, La Jolla, California; MedCalc, version 19.2, MedCalc Statistical Software, Ltd, Ostend, Belgium).

3 | RESULTS

3.1 | Patient characteristics of cat study population

Of the 1400 cats, 1047 (74.8%) became euthyroid, 57 (4.1%) became overtly hypothyroid, 240 (17.1%) became subclinically hypothyroid, and 56 (4%) cats remained hyperthyroid.[7]

Cats with overt and subclinical hypothyroidism were older and cats with persistent hyperthyroidism were younger than the euthyroid cats (Table 1). A higher proportion of hypothyroid cats (overt and subclinical) were female, compared to euthyroid cats (Table 1). None of the other signalment variables differed among the 4 outcome groups.

3.2 | Pretreatment serum T_4, T_3, and TSH concentrations

Hypothyroid cats had lower pretreatment serum T_4 and T_3 concentrations than did the euthyroid or persistently hyperthyroid cats

TABLE 4 Comparing the severity of disease and percent ^{131}I uptake in 1400 hyperthyroid cats, divided into 4 outcome groups

Variable	All cats (1400)	Euthyroid (1047)	Overt hypothyroid (57)	Subclinical hypothyroid (240)	Persistent hyperthyroid (56)	*P* value
Severity of disease						
Mild (<1.8 mCi)	596 (42.6%)	457^{a} (43.6%)	28^{b} (49.1%)	104^{c} (43.3%)	7^{a,b,c} (12.5%)	<.001*
Moderate (1.8-2.5 mCi)	538 (38.4%)	397 (37.9%)	20 (35.1%)	101 (42.1%)	20 (35.7%)	.59
Severe (>2.5 mCi)	266 (19.0%)	193^{a} (18.4%)	9^{b} (15.8%)	35^{c} (14.6%)	29^{a,b,c} (51.8%)	<.001*
24-hour percent ^{131}I uptake						
Low ^{131}I uptake (<16%)	261 (18.6%)	216^{a,b} (20.6%)	0^{a,c,d} (0%)	27^{b,c,e} (11.3%)	20^{e} (35.7%)	<.001*
Intermediate ^{131}I uptake (16%-28%)	818 (58.4%)	622 (59.4%)	30 (52.6%)	131 (54.6%)	27 (50%)	.39
High ^{131}I uptake (>28%)	321 (22.9%)	209^{a,b} (20.0%)	27^{a,c} (47.3%)	82^{b,d} (34.2%)	9^{c,d} (16.1)	<.001*

Note: Severity of disease based on ^{131}I dose or severity scores. Data are expressed as number and percent of cats. Values with the same superscript letters are significantly different to one another.

*Chi-square test, followed by the Holm-Bonferroni correction procedure for within group comparison.

(Table 1). In contrast, cats with persistent hyperthyroidism had higher serum T_4 and T_3 concentrations than did the hypothyroid or euthyroid cats.

Thirty-four (2.4%) of the 1400 hyperthyroid cats had detectable serum TSH concentrations (≥0.03 ng/mL). Of those, 15/34 cats (44.1%) had a history of methimazole treatment, whereas 19/34 cats (55.9%) had received no methimazole. In all 15 methimazole-treated cats, the drug had been discontinued 7 to 80 days before testing (median, 45 days; IQR, 14-60 days). Of the 34 cats with detectable serum TSH concentrations, 23 (67.4%) had mild hyperthyroid disease, 10 (29.4%) had moderate disease, and 1 (2.9%) had severe disease.

Hypothyroid cats had a higher prevalence of detectable serum TSH concentrations (≥0.03 ng/mL) than did the euthyroid or persistently hyperthyroid cats (Table 1). None of the cats with persistent hyperthyroidism had a detectable serum TSH concentration.

3.3 | Thyroid scintigraphy findings

Euthyroid cats had an approximately equal ratio of bilateral to unilateral thyroid disease (ie, "hot" thyroid nodules), whereas hypothyroid and persistently hyperthyroid cats more frequently had bilateral disease (Table 2). Most hyperthyroid cats with bilateral disease had a heterogenous (patchy) distribution of $^{99m}TcO_4^-$ uptake, but cats in the hypothyroid outcome group were more likely to have bilateral, homogeneous uptake of the radionuclide (Table 2).

Cats with persistent hyperthyroidism had higher TcTU, as compared to euthyroid and hypothyroid cats (Table 2). Likewise, cats with persistent hyperthyroidism had the highest values for all ratios (ie, ratios of thyroid count density to the salivary or background count densities) used to quantify increased thyroid activity, including the thyroid-to-salivary gland ratio (T/S), thyroid-to-axillary background ratio (T/A), thyroid-to-tracheal (T/T) background ratio, and thyroid-to-heart (T/H) background ratio (Table 2).[10,11] Cats with persistent hyperthyroidism also had higher thyroid tumor volume compared to euthyroid and hypothyroid cats (Table 2).

3.4 | Individualized ^{131}I dose calculations and percent ^{131}I uptake measurements

Persistently hyperthyroid cats had higher thyroid hormone scores, TcTU scores, and thyroid volume scores than either the euthyroid cats or cats with subclinical or overt hypothyroidism (Table 3). None of these 3 individual scores differed between the euthyroid or hypothyroid cats. Similarly, persistently hyperthyroid cats had higher composite ^{131}I dose scores than did euthyroid cats or cats with subclinical or overt hypothyroidism. Again, the composite ^{131}I dose score did not differ between euthyroid and hypothyroid cats (Table 3).

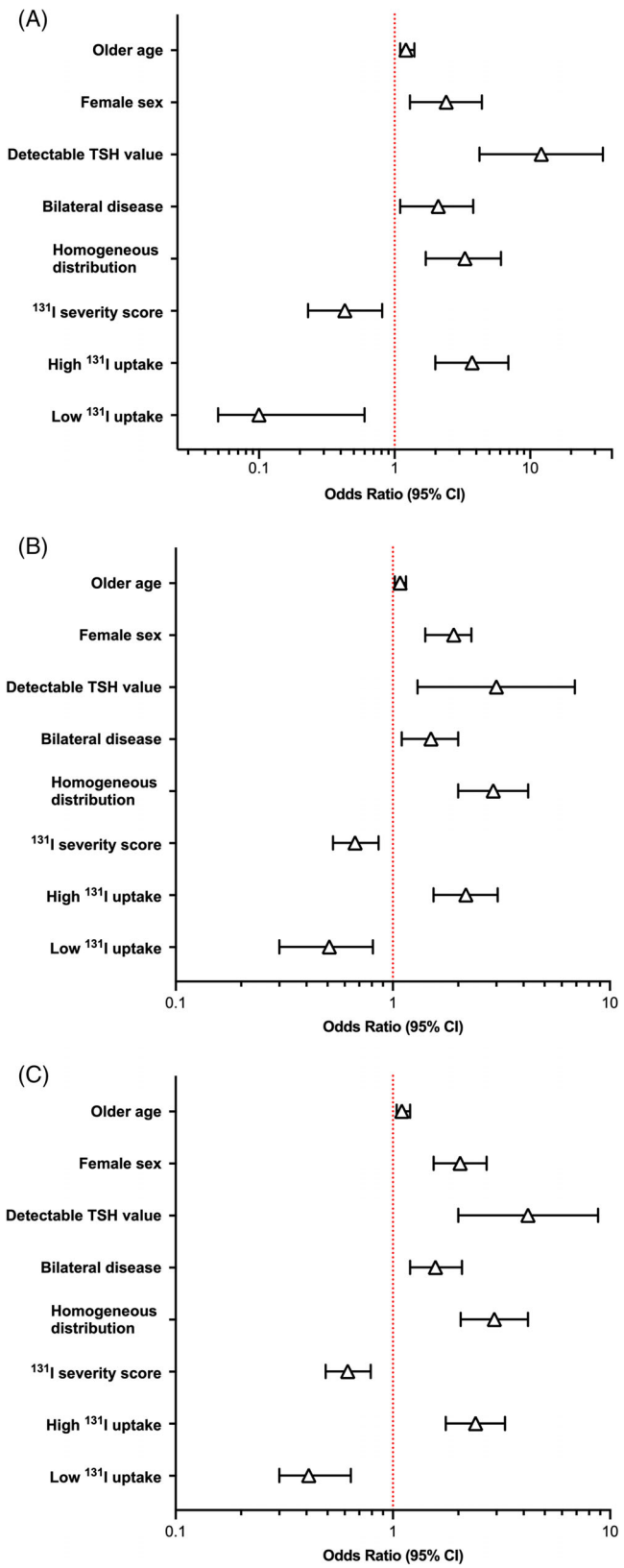
Cats with subclinical or overt hypothyroidism had higher 24-hour ^{131}I uptake results than did euthyroid or persistently hyperthyroid cats (Table 3). Overtly hypothyroid cats had higher ^{131}I uptake than did cats with subclinical hypothyroidism. In contrast, persistently hyperthyroid cats had lower ^{131}I uptake than did euthyroid or hypothyroid cats (Table 3).

Hypothyroid cats had a lower final calculated ^{131}I dose than either the euthyroid or persistently hyperthyroid cats (Table 3). The ^{131}I dose did not differ between cats with subclinical or overt hypothyroidism. In contrast, persistently hyperthyroid cats received a higher final ^{131}I dose than did euthyroid or hypothyroid cats (Table 3).

3.5 | Severity of hyperthyroid disease and percent ^{131}I uptake

When the 1400 hyperthyroid cats were divided into 3 severity groups based on their average ^{131}I dose score, 43% had mild disease, 38% had moderate disease, and 19% had severe disease (Table 4). Cats remaining persistently hyperthyroid were 3.5 times less likely to have mild disease (12.5% vs 44%) and 3 times more likely to have severe disease (52% vs 18%), as compared with euthyroid or hypothyroid cats ($P < .001$). However, of the 266 cats with severe disease, most

became euthyroid (n = 193; 72.6%) or hypothyroid (n = 44; 16.5%), with only 29 of the severely diseased cats (10.9%) remaining hyperthyroid after ^{131}I treatment.



When the 1400 hyperthyroid cats were divided into 3 groups based on their 24-hour percent ^{131}I uptake values, 19% had low uptake, 58% had midrange uptake, and 23% had high uptake (Table 4). Hypothyroid cats were 2 to 4 times less likely to have low uptake (9% vs 21%-34%) and 2 times more likely to have high uptake (35% vs 16%-20%), as compared with euthyroid and persistently hyperthyroid cats. In contrast, over a third (19 of 56; 34%) of persistently hyperthyroid cats had low ^{131}I uptake. Of these, 7/7 cats with mild disease, 8/20 (40%) with moderate disease, and 4/29 (13.7%) with severe disease had low ^{131}I uptake.

3.6 | Odds ratios for predicting treatment outcome

Multivariable logistic regression analysis identified multiple pretreatment factors that were associated with treatment outcome (Figures 1 and 2). Overtly hypothyroid cats were more likely to be older (OR = 1.21; 95% CI, 1.07-1.40; P = .003), female (OR = 2.37; 95% CI, 1.27-4.41; P = .007), have detectable serum TSH concentrations (OR = 12.06; 95% CI, 4.23-34.4; P < .001), have bilateral thyroid nodules (OR = 2.06; 95% CI, 1.10-3.84; P = .02), have homogeneous, bilateral uptake of $^{99m}TcO_4^-$ (OR = 3.27; 95% CI, 1.72-6.22; P < .001), have milder severity score (OR = 0.43; 95% CI, 0.23-0.81; P = .008), and have higher ^{131}I uptake (OR = 3.73; 95% CI, 2.02-6.88; P < .001; Figure 1A). Similarly, subclinically hypothyroid cats tended to be older (OR = 1.08; 95% CI, 1.02-1.15; P = .01), be female (OR = 1.91; 95% CI, 1.41-2.28; P < .001), have bilateral thyroid nodules (OR = 1.77; 95% CI, 1.09-1.97; P = .01), have homogeneous, bilateral distribution of $^{99m}TcO_4^-$ (OR = 2.87; 95% CI, 1.97-4.20; P < .001), have milder severity score (OR = 0.67; 95% CI, 0.53-0.86; P = .001), and have higher ^{131}I uptake (OR = 2.17; 95% CI, 1.54-3.04; P = .004; Figure 1B). The ORs for all 297 hypothyroid cats (combined group of 57 cats with overt and 240 cats with subclinical hypothyroidism) were intermediate, as compared with the overt and subclinical groups (Figure 1C).

Persistently hyperthyroid cats had many predictive factors that contrasted with the hypothyroid cats (Figure 2). Predictors included younger age (OR = 0.81; 95% CI, 0.72-0.92; P < .001), higher severity score (OR = 1.87; 95% CI, 1.51-2.31; P < .001), and lower ^{131}I uptake (OR = 3.5; 95% CI, 1.8-6.80; P = .001).

FIGURE 1 Forest plots showing odds ratio and 95% CI of pretreatment factors contributing to iatrogenic hypothyroidism. (A) Overt hypothyroidism; (B) Subclinical hypothyroidism; (C) Both overt and subclinical hypothyroidism, combined. Multivariable logistic regression indicated the following 8 predictors: older age; female sex; detectable serum TSH concentration; bilateral thyroid disease; symmetrical, homogeneous distribution of $^{99m}TcO_4^-$ uptake into both thyroid lobes; ^{131}I severity score (based on serum T_4 and T_3 concentrations, thyroid tumor volume, and percent TcTU); low ^{131}I thyroid uptake (<16%); and high ^{131}I thyroid uptake (>28%). CI, confidence interval; TcTU, percent thyroidal uptake of sodium ^{99m}Tc-pertechnetate; TSH, thyroid-stimulating hormone

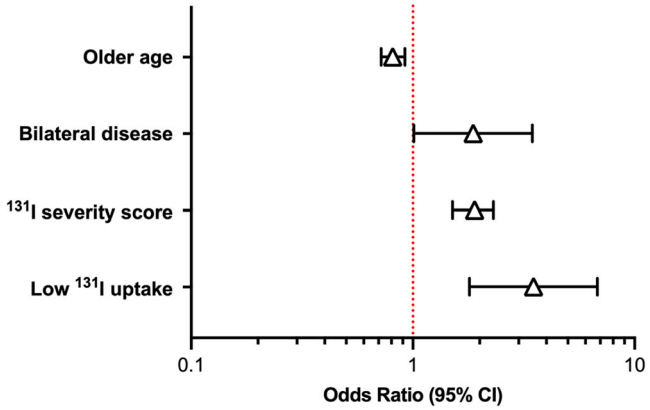


FIGURE 2 Forest plots showing odds ratio and 95% CI of pretreatment factors contributing to persistent hyperthyroidism (treatment failure). Multivariable logistic regression indicated the following 3 predictors: younger age; bilateral thyroid disease; higher ^{131}I severity score; and low ^{131}I thyroid uptake (<16%). CI, confidence interval

4 | DISCUSSION

We identified several pretreatment factors that helped predict which cats would develop iatrogenic hypothyroidism or fail ^{131}I treatment and remain persistently hyperthyroidism using our novel dosing algorithm. Cats likely to develop ^{131}I-induced hypothyroidism tended to be older, female, have detectable serum TSH concentration, bilateral thyroid disease (especially with homogeneous distribution of $^{99m}TcO_4^-$, uptake), milder severity, and higher 24-hour percent ^{131}I uptake. Conversely, cats likely to remain persistently hyperthyroid tended to be younger and have higher severity and lower ^{131}I uptake. Our findings suggest that these predictive factors be considered when treating cats with ^{131}I, at least when using our individualized ^{131}I dosing algorithm, calculated to administer the lowest effective dose possible.[7] Slightly decreasing or increasing the algorithm's final calculated dose in cats at risk for hypothyroidism or treatment failure, respectively, might improve treatment outcomes and result in a higher rate of euthyroidism.

Our finding that older cats were slightly more likely to become hypothyroid after ^{131}I agrees with findings in some studies of human patients with hyperthyroidism.[25] Although the mechanism is unclear, this observation suggests that the thyroid tissue of older cats may be more susceptible to the ablative effects of ^{131}I, whereas younger cats are more resistant to ^{131}I. Female cats were twice as likely than males to develop iatrogenic hypothyroidism, a finding that also has been reported in several studies of human patients.[26-29] From a biological point of view, why the normal or adenomatous thyrocytes of male and female cats would differ in their radiosensitivity is not understood, especially because all of our cats had been neutered as young adults (junior to prime life stage[30]). Further study of the effect of sex on the response to ^{131}I in cats is needed.

Our study confirms that cats with detectable serum TSH concentrations (≥0.03 ng/mL) are at much higher risk for development of ^{131}I-induced hypothyroidism. The cats that developed more severe (overt) hypothyroidism had a much higher OR (12.1) than did the cats with milder (subclinical) hypothyroidism (3.0). An undetectable serum TSH concentration (<0.03 ng/mL) is expected in hyperthyroid cats because of the negative-feedback effects of their high circulating T_4 and T_3 concentrations on pituitary TSH secretion.[8] As circulating TSH concentrations become suppressed in cats with hyperthyroidism, any normal (ie, nonadenomatous) thyroid tissue will atrophy, as both thyroidal iodine uptake and organification decrease.[31] In contrast, iodine uptake, growth, and hyperfunction of the hyperthyroid cat's thyroid tumor nodules are not dependent on TSH stimulation.[32,33] Therefore, finding a detectable serum TSH concentration indicates that any remaining normal thyroid tissue will likely take up and concentrate ^{131}I, increasing the risk for ablation of normal thyrocytes and iatrogenic hypothyroidism.[34,35] Because treatment with methimazole lowers serum thyroid hormone concentrations and may allow previously suppressed pituitary thyrotropes to secrete normal or increased amounts of TSH,[35,36] we discontinued methimazole for at least 1 week before ^{131}I treatment in all of our cats. With this regimen, we have previously reported that serum TSH concentrations were suppressed in 98% of hyperthyroid cats,[8] similar to the results of our current study. Most cats with detectable serum TSH concentrations in the current and previous study[8] had mild hyperthyroid disease, which suggests that TSH suppression might occur if hyperthyroidism is allowed to progress to a more severe stage. In any case, if serum TSH concentrations are measurable and the cat must be treated, the clinician should consider lowering the ^{131}I dose administered.

Hyperthyroid cats with bilateral thyroid disease were 1.5 times more likely to develop ^{131}I-induced hypothyroidism than cats with unilateral thyroid nodules, consistent with previous observations.[37] Given the limited range of radioiodine's ablative β-particles (average path length, 0.4-1 mm),[38,39] it is reasonable to expect that cats with unilateral thyroid gland disease (in which no adenomatous tissue is present in the normal thyroid lobe) would be less likely to develop hypothyroidism after ^{131}I treatment because the dormant, nonadenomatous thyroid lobe should be outside the range of the ablative ^{131}I β-particles concentrated within adenomatous thyroid tumor. In addition, cats with unilateral thyroid adenomas have more normal thyroid tissue than do cats with bilateral thyroid disease, which may have only minimal amounts of normal thyroid tissue (at least a few clusters of "normal" atrophied thyroid follicles can almost always be identified within each adenomatous lobe).[40,41]

Even more important than bilateral thyroid disease alone, cats that had a bilateral symmetrical uptake pattern on thyroid scintigraphy (ie, homogeneous or symmetrical uptake of $^{99m}TcO_4^-$ into both thyroid lobes) were 3 times more likely to develop ^{131}I-induced hypothyroidism. The finding that cats with bilaterally symmetrical lesions are at higher risk for developing hypothyroidism is consistent with the hypothesis proposed previously.[37] The reason why those authors found no difference in ^{131}I-induced hypothyroid rates between cats with bilateral-symmetrical and bilateral-asymmetrical scintigraphic patterns is likely related to the small number of cats with bilateral-symmetrical disease (9 cats in the previous study[37] vs 185 cats in our

study) and the higher ^{131}I doses used (median, 4.3 mCi vs 1.9 mCi in our study, respectively). In some respects, this bilateral symmetrical pattern of uptake is similar to the situation in Graves' disease in people, where the hyperplastic thyrocytes of both thyroid lobes take up ^{131}I diffusely and hypothyroidism is almost inevitable.[28,29,42] Our observation that cats with an asymmetrical (heterogeneous) $^{99m}TcO_4^-$ uptake pattern were less likely to develop ^{131}I-induced hypothyroidism likely relates to the lower radiation dose delivered to the thyroid nodule with less intense ^{131}I uptake, which may help preserve more of the dormant or normal thyrocytes within that adenomatous lobe.

Hyperthyroid cats with more severe disease (based on higher ^{131}I dose or severity score) were more likely to fail treatment and remain persistently hyperthyroid. This finding agrees with other reports in cats[3,5,6,43-45] and humans[26,28,46-49] in which individuals with higher serum T_4 concentration, larger goiters, or more severe hyperthyroidism were more likely remain hyperthyroid. In contrast, hyperthyroid cats with milder disease were more likely to develop ^{131}I-induced hypothyroidism, similar to other reports in ^{131}I-treated cats.[3] Because the ^{131}I severity score serves as the basis for the dose calculation in our algorithm, these findings suggest we may need to slightly adjust our dose calculations in cats likely to fail ^{131}I treatment or develop hypothyroidism. However, most cats with severe disease (237 of 266; 89%) became euthyroid or hypothyroid when dosed according to our algorithm (Table 4). Similarly, most cats with mild hyperthyroidism (457 of 596; 77%) did not develop hypothyroidism when dosed according to our algorithm.

Cats with high 24-hour ^{131}I thyroid uptake (>28%) had a 2 to 4 times higher risk for development of ^{131}I-induced hypothyroidism. Cats that developed more severe (overt) hypothyroidism had a higher OR (3.7) than did cats with milder (subclinical) hypothyroidism (2.2). That higher ^{131}I thyroid uptake may predispose cats to hypothyroidism is consistent with reports in human patients with toxic nodular goiter (adenomatous nodules).[25] The higher uptake of ^{131}I into the nodule(s) delivers higher amounts of ablative β-radiation to both the adenomatous tissue, as well as any adjacent normal thyroid tissue, and that higher amount of radiation may be sufficient to destroy the normal tissue together with the adenomatous nodules. In contrast, cats with low ^{131}I uptake (<16%) were at 3.5 times higher risk for failing treatment and remaining hyperthyroid. In this instance, treatment failure likely results because the dose of β-radiation delivered to the adenomatous thyroid nodules was inadequate to completely ablate the adenoma(s). Again, we saw this outcome even though our algorithm adjusts the ^{131}I dose based on ^{131}I uptake. These findings suggest we may need to change the weighting applied to ^{131}I uptake when calculating the final dose, especially in cats with high ^{131}I uptake, in which 109/209 (52%) developed hypothyroidism (Table 4). In cats with low uptake, on the other hand, only 20/216 (9.2%) failed treatment when dosed according to our algorithm. Regardless, these difference in ^{131}I treatment responses would likely be much higher in standard ^{131}I treatment protocols that do not measure the percent ^{131}I uptake to adjust the final ^{131}I dose administered.

We cannot exclude the possibility that some hyperthyroid cats that failed ^{131}I treatment were suffering from thyroid carcinoma, because we did not biopsy thyroid glands in any of our cats. For this study, we excluded all cats with multifocal thyroid disease (>3 thyroid nodules on thyroid scintigraphy), a common feature of thyroid carcinoma,[12,13] but thyroid scintigraphy cannot always differentiate between thyroid adenoma and carcinoma, and it is possible for cats with unilateral or bilateral cervical tumors to have pathological evidence of thyroid carcinoma.[12,50,51] However, almost all of our 56 cats that remained persistently hyperthyroid did show a partial response to low doses of ^{131}I; 33 these cats (59%) had a decrease in serum T_4 concentration of ≥50% whereas 89% of cats had a decrease in serum T_4 concentration of at least 30%. Such partial responses to low-dose ^{131}I treatment might not be expected in cats with thyroid carcinoma, which require ^{131}I doses 8- to 10-fold higher than those used for thyroid adenoma.[51-53] In addition, 28 of the of our 56 cats that failed initial ^{131}I treatment were retreated using the same protocol (median retreatment dose, 2.1 mCi; range, 1.4-5.6 mCi). Of these, 27 (96%) of 28 became euthyroid after retreatment. In human patients with ^{131}I-refractory thyroid carcinoma, the most common reason for treatment failure is poor ^{131}I uptake (usually resulting from loss of function of the sodium iodide symporter on the surface of the thyroid follicular cell).[54,55] Our single cat that failed retreatment (with 2.5 mCi) also had very low ^{131}I uptake measurement (9.5%), consistent with the possibility of a small thyroid carcinoma.

In summary, we identified several pretreatment findings that helped predict which cats were likely to develop iatrogenic hypothyroidism or fail ^{131}I treatment and remain hyperthyroid. The findings that detectable serum TSH concentration, pattern of thyroid tumor disease and $^{99m}TcO_4^-$, uptake, disease severity, and percent ^{131}I uptake can help predict outcome suggest that these factors be considered when treating cats with ^{131}I, regardless of the protocol used. Additional clinical research is needed to determine if decreasing or increasing the dose in cats at risk for hypothyroidism or treatment failure, respectively, will result in a higher rate of euthyroidism.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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