Prognostic value of serum total thyroxine concentration at admission to an intensive care unit for critically ill dogs

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OBJECTIVE

To determine whether serum total thyroxine (TT4) concentration at admission to an intensive care unit (ICU) was associated with mortality rate and duration of hospitalization for critically ill dogs.

ANIMALS

166 client-owned dogs that were hospitalized in the ICU of a private veterinary practice from January 2013 through December 2016 and for which serum TT4 concentration had been measured at admission.

PROCEDURES

Medical records were reviewed to collect data regarding patient signalment, concurrent illnesses, medications, reason for hospitalization, outcome (death, euthanasia, or survival to hospital discharge), duration of hospitalization, and initial serum TT4 concentration.

RESULTS

Mean age of the 166 dogs was 8.6 years (range, 1 to 16 years). Overall mortality rate was 15.7%, with 26 dogs failing to survive to hospital discharge. Of these 26 dogs, 7 died and 19 were euthanized. No significant association was identified between serum TT4 concentration at admission and survival to discharge (yes or no) or duration of hospitalization. Age was significantly associated with survival to discharge, with older dogs less likely to survive than younger dogs. Duration of hospitalization was also associated with survival to discharge, with longer hospital stays associated with a lower likelihood of survival to discharge.

CONCLUSIONS AND CLINICAL RELEVANCE

Findings suggested that serum TT4 concentration at admission to an ICU had no prognostic value in this population of critically ill dogs. (*J Am Vet Med Assoc* 2020;257:57–61)

Nonthyroidal illness syndrome has been described as alterations in circulating thyroid hormone concentrations that occur in euthyroid patients owing to concurrent illness.[1–3] Several mechanisms contribute to this condition, including low secretion of TSH, low synthesis of TT4, low concentrations of circulating thyroid gland–binding proteins or low thyroid gland–binding affinities to these proteins, presence of serum protein binding inhibitors, and inhibition of deiodination of thyroxine to triiodothyronine in the peripheral tissues.[2,4] In hospitalized people, a relationship has been established between thyroid hormone status and outcome.[2,4–6] The most common thyroid hormone abnormalities in people with NTIS are a low serum triiodothyronine concentration, low to normal serum thyroxine concentration, high serum reverse-triiodothyronine concentration, and unremarkable serum TSH concentration.[4] However, with more severe systemic illness, decreases in serum TT4 and free thyroxine concentrations can occur.[7] In dogs, the magnitude of the changes in thyroid hormone concentrations is typically related to severity of the illness but not to the category of disease.[8,9] This observation is believed to represent a physiologic adaptation that decreases cellular metabolism during illness.[2]

ABBREVIATIONS

ICU	Intensive care unit
LOD	Limit of detection
NTIS	Nonthyroidal illness syndrome
TSH	Thyroid-stimulating hormone
TT4	Total thyroxine

In dogs with NTIS, the serum TT4 concentration is most commonly low, with variable changes in serum triiodothyronine, free thyroxine, and TSH concentrations.[8–12] However, given the lack of a highly sensitive and accurate assay for serum TSH concentration in dogs, conflicting information on what constitutes a diagnosis of NTIS, and diverse conclusions on the value of such alterations in predicting patient outcome, it has been difficult to examine the relationship between thyroid hormone concentrations and disease severity.

Serum TT4 concentration is a commonly measured analyte in reference laboratory serum biochemical panels and may be an easy and useful predictor of mortality rate in veterinary patients admitted to an ICU. If this were true, clinicians might be able to provide more accurate prognostic information to clients and determine which patients are at higher risk of death, requiring more intensive monitoring and earlier intervention.

The objective of the study reported here was to determine whether serum TT4 concentration at ad-

mission to an ICU was associated with mortality rate in critically ill dogs, independent of the underlying cause of alterations in this analyte. A secondary objective was to determine whether serum TT4 concentration at admission was related to the duration of hospitalization. We hypothesized that lower TT4 values at admission would be associated with a higher mortality rate and longer hospital stays.

Materials and Methods

Animals

The medical records of the VCA West Los Angeles Animal Hospital were evaluated to identify dogs that were hospitalized from January 2013 through December 2016 for which serum TT4 concentration, a component of the hospital's comprehensive serum biochemical panel commonly ordered at hospital admission, was measured at the time of admission to the ICU. This time frame was chosen to ensure that the same assay had been used for all dogs. Records were cross-referenced to identify dogs within this population that had been hospitalized in the ICU under codes corresponding to the 2 highest levels (levels 3 and 4) of intensive care at the hospital **(Appendix)** and for which hands-on monitoring and intervention were performed at a minimum frequency of every 5 to 10 minutes. If multiple admissions were recorded for a given patient during the study period, only data pertaining to the initial admission were included.

Dogs were excluded from the study if they were < 1 year of age, were a sight hound breed, had known alterations in hypothalamic-pituitary-thyroid axis function, had an incomplete medical record, or had received within 3 months prior to admission any of the following medications known to alter thyroid hormone secretion: glucocorticoid drugs (including topical or ophthalmic preparations), amiodarone, phenobarbital, zonisamide, carbamazepine, phenytoin, bromocriptine, levodopa, lithium, dopamine, rifampicin, 5-fluorouracil, high-dose salicylates, propranolol, levothyroxine, methimazole, or sulfonamides.[2,3,13]

Data collection

Data were collected from the medical records regarding patient signalment (age, sex, and breed), concurrent illnesses and medications, reason for hospitalization, outcome (death, euthanasia, or survival to discharge), duration of hospitalization, initial serum TT4 concentration, and other thyroid hormone data (if available). The reason for hospitalization was categorized as trauma, respiratory disease, gastrointestinal disease, reproductive disease, neoplasia, hematologic disease, cardiovascular disease, urinary disease, hepatic disease, and miscellaneous disease.

Thyroid hormone assay

For the serum biochemical profiles, blood samples were collected from a jugular, cephalic, or saphenous vein via 1-inch, 20-gauge needles into serum-separator containers for analysis at a commercial laboratory.[a] Samples were stored at 4°C and transported to the laboratory within 12 hours after collection. Serum TT4 concentration was analyzed within 24 to 48 hours after sample collection by use of an enzyme immunoassay.[b] Intra-assay and interassay coefficients of variation were 4.3% and 8%, respectively, and the lower LOD was 0.5 µg/dL. Results less than this lower LOD were assigned a value of 0.5 µg/dL. The reference range for serum TT4 concentration measured with this assay was 0.8 to 3.5 µg/dL.

Statistical analysis

Statistical software[c] was used for data analysis. Because of the large sample size, normal distribution of data was assumed. Analysis of variance was used to compare mean values of dog age and serum TT4 concentration between dogs grouped by survival status or reason for hospitalization. Linear regression and logistic regression were performed to evaluate associations between serum TT4 concentration and duration of hospitalization or the likelihood of survival to discharge, respectively. Values of $P \leq 0.05$ were considered significant, and all statistical tests were 2-tailed.

Results

During the 4-year study period, a total of 2,933 dogs were admitted to the ICU and hospitalized under the 2 highest levels of intensive care. In 465 of the 2,933 dogs, serum TT4 concentration was measured at the time of admission to the ICU. After exclusion criteria were applied, 166 dogs remained for inclusion in the study.

Seventy-four of the 166 (44.6%) dogs were female (63 spayed and 11 sexually intact), and 92 (55.4%) were male (78 neutered and 14 sexually intact). The mean age was 8.6 years (median, 10 years; range, 1 to 16 years). Mixed-breed dogs were common (n = 45 [27%]), and the most common breeds were Labrador Retriever (11 [6.6%), Yorkshire Terrier (9 [5.4%]), Chihuahua (8 [4.8%]), and Maltese (6 [3.6%]). The most common specific reasons for hospitalization were gastrointestinal disease (n = 46 [27.7%]), respiratory disease (25 [15.1%]), and trauma (21 [12.7%]; **Table 1**).

Overall, 140 (84.3%) dogs survived, and 26 (15.7%) dogs failed to survive to discharge from the

Table 1—Mean ± SD serum TT4 concentration at admission to an ICU for 166 dogs grouped by reason for hospitalization.

Reason for hospitalization	TT4 (µg/dL)
Gastrointestinal disease (n = 46)	1.0 ± 0.5
Respiratory disease (n = 25)	0.9 ± 0.5
Trauma (n = 21)	1.0 ± 0.4
Reproductive disease (n = 4)	0.6 ± 0.1
Neoplasia (n = 17)	1.2 ± 0.6
Hematologic disease (n = 7)	0.6 ± 0.2
Cardiovascular disease (n = 16)	1.2 ± 0.4
Urinary disease (n = 5)	0.9 ± 0.7
Hepatic disease (n = 3)	0.5 ± 0.0
Miscellaneous disease (n = 22)	1.1 ± 0.5

hospital (7 died [3 within the first 24 hours after admission] and 19 were euthanized). Mean ± SD duration of hospitalization for these 2 groups was 3.3 ± 2.2 days and 2.2 ± 1.3 days, respectively. Survival and mortality rates were summarized by reason for hospitalization **(Figure 1)**.

Mean ± SD serum TT4 concentration at admission to the ICU was 1.0 ± 0.5 µg/dL (median, 0.9 µg/dL; range, 0.5 to 2.3 µg/dL). For 69 (41.6%) dogs, this concentration was lower than the reference range, and 39 of these dogs had TT4 concentrations less than the lower LOD of the assay (ie, < 0.5 µg/dL). Mean values for serum TT4 concentration were summarized by reason for hospitalization (Table 1).

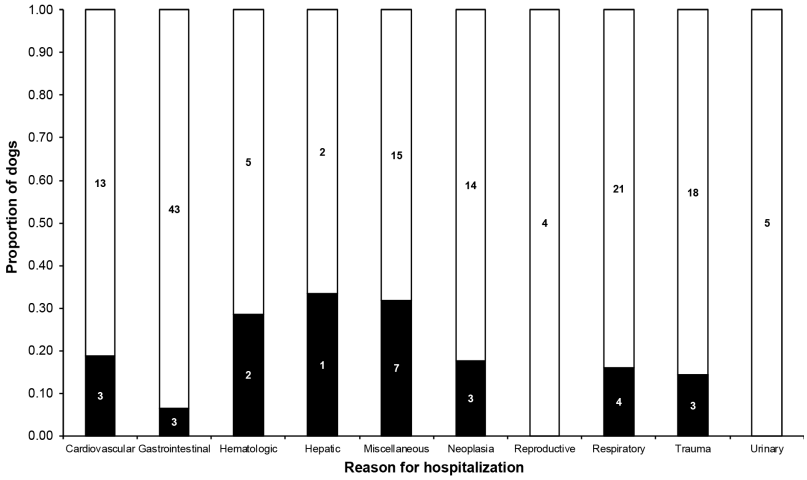

Figure 1—Proportions of dogs that survived (white portion of bars) or failed to survive (black portion) to discharge following admission to an ICU, by reason for hospitalization (ie, disease category). Numbers within the bars represent the number of dogs in each category.

Associations with serum TT4 concentration

No significant difference in serum TT4 concentration at admission was identified between dogs that survived and those that failed to survive to discharge from the hospital (P = 0.19; **Figure 2**) or between dogs that died and dogs that were euthanized (P = 0.51). No significant association was identified between serum TT4 concentration and duration of hospitalization.

Dogs hospitalized for treatment of cardiovascular diseases had a significantly higher serum TT4 concentration at admission than did those treated for hematologic diseases (P = 0.02), hepatic diseases (P = 0.03), and reproductive diseases (P = 0.04). Dogs hospitalized for treatment of gastrointestinal diseases had a significantly (P = 0.03) higher serum TT4 concentration at admission than did those treated for hematologic diseases. Dogs hospitalized for treatment of miscellaneous diseases had a significantly (P = 0.03) higher serum TT4 concentration at admission than did those treated for hematologic diseases. Dogs hospitalized for treatment of neoplastic diseases had a significantly higher serum TT4 concentration at admission than did those treated for hematologic diseases (P = 0.01), hepatic diseases (P = 0.03), or reproductive diseases (P = 0.04).

Associations with survival to discharge

Older dogs were significantly (P = 0.002) less likely to survive to discharge than were younger dogs. Duration of hospitalization was also significantly (P = 0.11) associated with survival to discharge, with longer hospital stays associated with a higher likelihood of survival. This association remained after the 3 dogs that died within the first 24 hours after admission were removed from the analysis (P = 0.049).

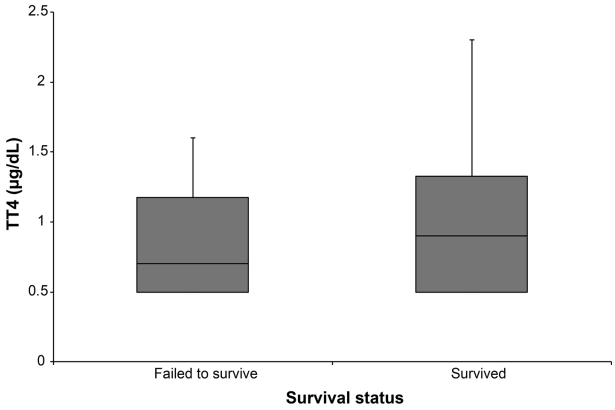

Figure 2—Box-and-whisker plots of serum TT4 concentrations at admission to an ICU for dogs that survived (n = 140) or failed to survive (26) to discharge from the hospital. Boxes represent the lower to upper quartiles (ie, 25th to 75th percentiles), the horizontal line with the boxes represents the median value, and whiskers represent the range. The minimum values and lower quartiles were the same for both groups of dogs.

Discussion

The goal of the present study was to determine whether serum TT4 concentration at admission to an ICU could be used as a prognostic factor for critically ill dogs. Our results indicated no association between that variable and survival to discharge or duration of hospitalization.

The evidence is conflicting as to the association between thyroid hormone alterations and the likelihood of survival for veterinary patients. Our findings were similar to those of another study[12] involving dogs with systemic inflammatory response syndrome or sepsis. Although abnormalities were found in serum thyroid hormone concentrations, no relationships were identi-

fied between these values and survival rates. Although hospitalization level codes, similar to those used in the present study to classify disease severity, were not evaluated as a possible predictor variable in that study,[12] the Acute Patient Physiologic and Laboratory Evaluation (APPLE[fast]) score was included and was the only variable predictive of a poor outcome.

The lack of an association between serum TT4 concentration at admission and the likelihood of survival to discharge could be attributed to several possible explanations, including the use of different analytic methods, source populations, disease categories, and case selection bias; this finding was dissimilar to previously reported findings.[9,14,15] The lower LOD of the serum TT4 assay used in the present study was 0.5 µg/dL, and our decision to assign a TT4 value of 0.5 µg/dL to samples with values below this limit (in total, 39 dogs) may have resulted in a greater number of patients having measurable TT4 concentrations than would have been had they been categorized as having a concentration below the lower LOD of the assay.

Another explanation for the observed differences between study findings could have been differences in the severity and duration of illness for the included dogs. As described previously, severity and duration of illness can affect serum thyroid hormone concentrations in people[2,7,16] and dogs.[8] Furthermore, by including a wide variety of patients hospitalized for different causes, we may have inadvertently included patients that were not truly as critically ill as were those included in other studies. However, the overall mortality rate of the patients in the present study was similar to that of other studies,[14,15] and we identified a significant relationship between duration of hospitalization and the likelihood of survival to discharge. In addition, to be included in the present study, dogs were required to have been hospitalized at level 3 or 4 and to have had a serum TT4 concentration measurement at admission to the ICU, representing a potentially biased group of patients. To address such bias, a prospective study would need to be performed wherein every dog admitted to the ICU would need to be tested for serum TT4 concentration, which might not be clinically practical or useful.

Limitations of the study reported here included its retrospective nature, a lack of objective quantification of critical illness, and a lack of a definitive diagnosis in many dogs. Although undiagnosed hypothyroidism was unlikely among the included dogs, the possibility that truly hypothyroid dogs might have been included cannot be dismissed. Another limitation was that the reasons for euthanasia were not always obvious on review of the medical records. Reasons for euthanasia can be complex, and owners were not asked for their rationale. Consequently, the possibility existed that some of the euthanized dogs might have survived had treatment been continued, which could have affected the results.

Regardless of any limitations, our results indicated that serum TT4 concentration at admission to an ICU was not significantly associated with the likelihood of survival to discharge or duration of hospitalization in critically ill dogs. A prospective study involving enrollment of dogs at admission to an ICU, additional objective critical illness scoring, and more thorough hypothalamic-pituitary-thyroid axis testing (requiring an improved canine serum TSH assay) is warranted to further evaluate thyroid hormone alterations in dogs and to determine whether such alterations in thyroid function may serve as clinically useful predictors of disease severity and mortality rate.

Footnotes

a. Antech Diagnostics, Irvine, Calif.
b. DRI thyroxine assay, Microgenic Corp, Freemont, Calif.
c. StatView, version 5.0, SAS Institute Inc, Cary, NC.

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Appendix

Description of hospitalization level codes used to categorize ICU patients.

Hospitalization level	Description
1	• Basic hospitalization for patients requiring care and observation while receiving surgical or medical attention • Vital parameters are regularly measured, but the patient is not receiving IV fluid therapy • Commonly used for routine day procedures • Patient visits by staff typically occur every 2 to 4 hours

2	• Appropriate for patients with level 1 requirements plus those receiving the following:
	  • Seizure monitoring
	  • Respiratory monitoring
	  • Cardiac monitoring
	  • IV fluid therapy or other IV infusions
	  • Blood transfusions
	• Patient visits by staff typically occur every 15 to 60 minutes

3	• Appropriate when the critical nature of a patient's condition requires frequent care
	• Appropriate for patients with level 2 requirements but with a greater degree of illness
	• Other factors that may reflect a greater degree of illness and meet the criteria of level 3:
	  • Diabetic ketoacidosis
	  • Renal failure
	  • Postoperative monitoring following major surgeries
	  • Pneumonia
	  • Bleeding disorders
	  • Oxygen supplementation
	  • Intermittent or continuous noninvasive mechanical monitoring
	• Patient visits by staff typically occur every 5 to 10 minutes

4	• Appropriate for patients requiring continual care and supervision (eg, mechanical ventilation)

Correction: Use of radiographic measurements to diagnose stage B2 preclinical myxomatous mitral valve disease in dogs

In the article "Use of radiographic measurements to diagnose stage B2 preclinical myxomatous mitral valve disease in dogs" (*J Am Vet Med Assoc* 2020;256:1129–1136), incorrect values are reported in the text for the combined variable of vertebral heart size and vertebral left atrial size (VHS + VLAS) at the cutoff that resulted in maximum specificity and for the positive predictive value (PPV) at that cutoff. The correct value for the VHS + VLAS cutoff that resulted in maximum specificity is 14.75 vertebral body units (VBUs), and the PPV at that cutoff is 93%. The values reported in Table 3 are correct.