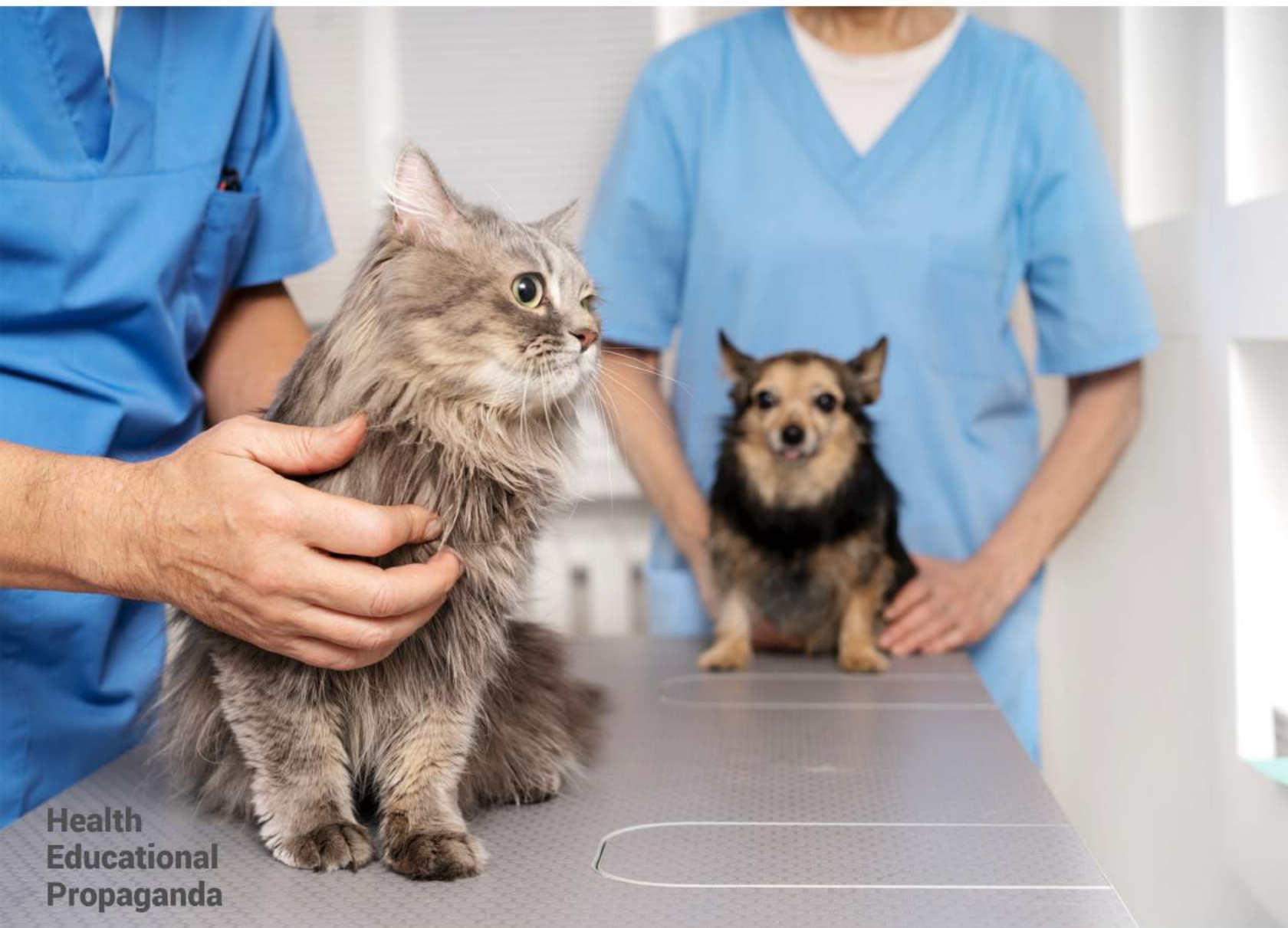




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# **The Relationship between Total T4 Concentration and Disease Severity and Mortality in Dogs and Cats with NTIS**



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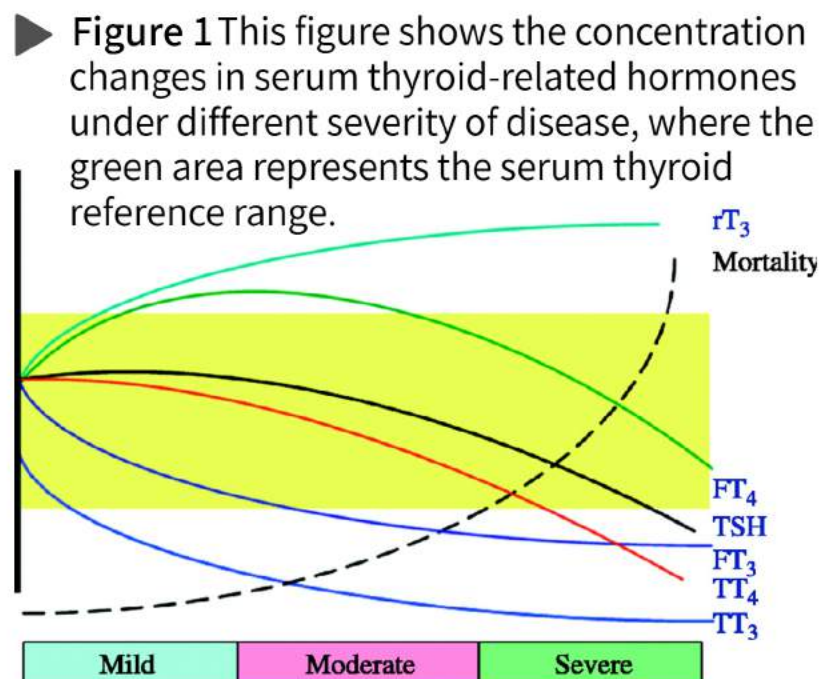
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As pets age, so do the problems of chronic disease. Clinically, there are more and more patients with chronic diseases in veterinary clinics, and many of them suffer from multiple chronic diseases. Through biochemical tests, the concentrations of various test items for patients can be obtained. With the assistance of multiple differential and diagnostic tools, it can also help diagnose and treat various chronic diseases, and assist and educate owners to care for pet patients. The following is a summary of the relationship between non-thyroid disease syndrome (NTIS) and the biochemical concentration of Total T4 (tT4) for canine and feline patients, as well as its clinical significance.

## What is non-thyroidal illness syndrome (NTIS)?

Non-thyroid disease syndrome refers to systemic diseases other than thyroid diseases, which directly affect thyroid function and lead to changes in the function of the hypothalamic-pituitary-thyroid (HPT) axis. NTIS is characterized by reduced serum thyroid hormone concentrations and reduced tissue supply, resulting from a combination of hypothyroidism and altered T4 and T3 metabolism. The meaning of its physiological mechanism is that when the circulating thyroid hormone in the body is low, it will theoretically cause negative feedback. However, due to central hypothyroidism, TSH secretion is inhibited, resulting in reduced tT4 and tT3 concentrations in NTIS patients. There is also evidence that due to the inhibition of type 1 5-deiodinase (deiodinase) activity or the decrease in the proportion of T4 entering deiodinated cells, this leads to a decrease in T3 in the circulation. In addition, thyroid-binding hormone inhibitors and inflammatory cytokines may also affect serum concentrations.



Note: Adapted from "Mechanisms behind the non-thyroidal illness syndrome: an update" by Maria H Warner and Geoffrey J Beckett, 2010, Journal of Endocrinology, 2010 Apr;205(1), P.2



## Predisposing Group for NTIS

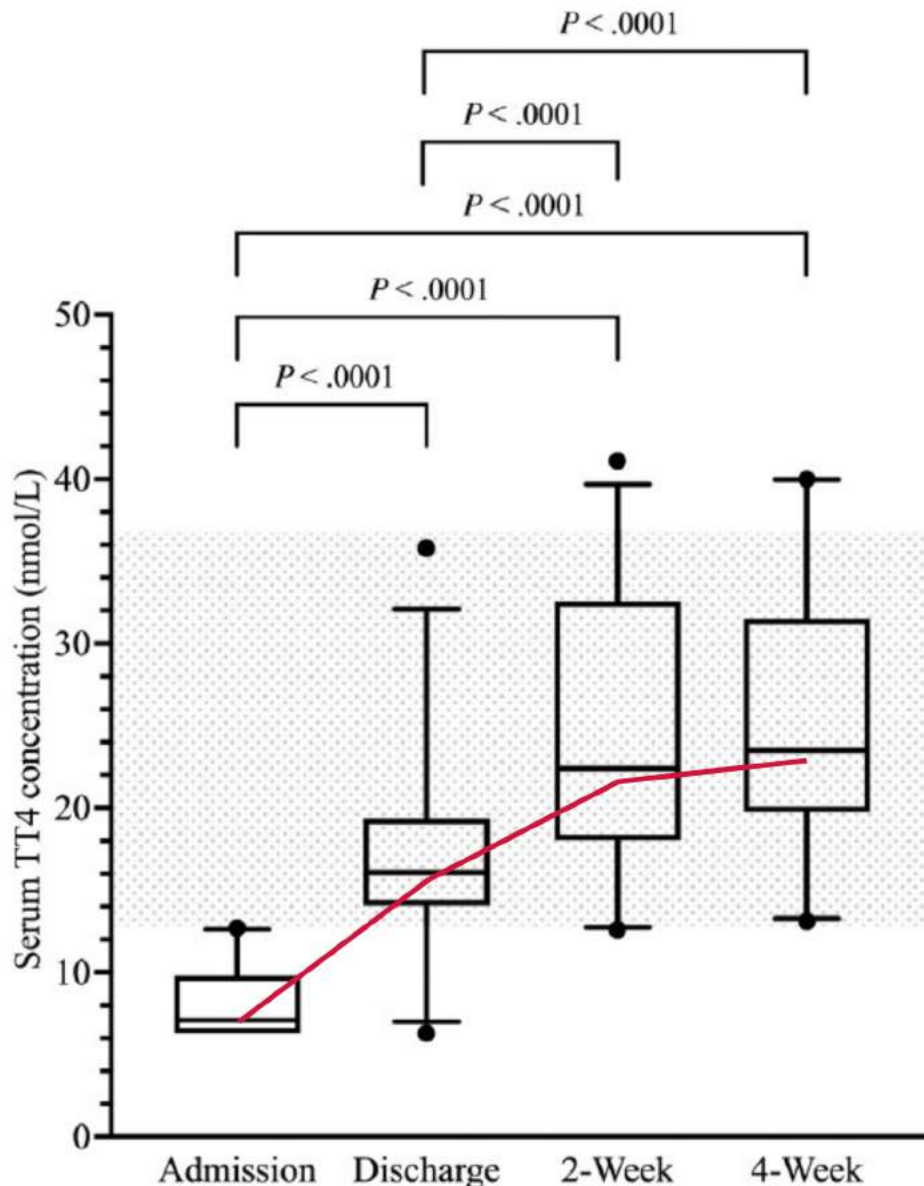
In human studies, NTIS is most commonly seen in emergency patients admitted to pediatric or neonatal intensive care units (ICUs). Starvation, trauma, or surgery can also cause a drop in thyroid hormones. NTIS can occur with any serious illness, and patterns of thyroid hormone changes are associated with the severity of the illness. In veterinary research, relevant research has been conducted on horses, dogs, and cats. NTIS is common in critically ill and premature young horses and is related to the severity of the disease and mortality. Many acute and chronic conditions, including endocrine, gastrointestinal, renal, oncological, and orthopedic diseases, can cause NTIS in dogs.

## Research on Dogs with NTIS: The Low tT4 Concentration among Dogs with NTIS Can Easily Lead to Misdiagnosis, and fT4 May Be Used as an Indicator of Normal Thyroid Function in Animals in the Acute Phase

Regarding changes in thyroid function in dogs with NTIS disease, in a 2023 research report in the Journal of Veterinary Internal Medicine, the research subjects used were dogs with acute illness (duration less than a week) and those that required hospitalization. Animals were evaluated and monitored from the acute phase to the recovery period after discharge (calculated as four weeks after discharge), and the changes in the tT4 measurement value of the test dogs were monitored. As shown in Figure 1 below, the results show that the tT4 value in the serum of the test dogs was low during NTIS. This may lead to veterinarians misdiagnosing the disease as hypothyroidism and giving unnecessary thyroid hormone supplements to euthyroid dogs. During the recovery period of the test dogs, serum concentrations of tT4, tT3, and TSH increased, while the tT4/TSH ratio did not change, indicating that increased TSH secretion allowed thyroid hormones to return to normal function. This study also confirms previous findings that serum fT4 concentrations are minimally affected in dogs with NTIS,

indicating that fT4 concentrations measured by equilibrium dialysis (ED) are most likely to represent thyroid function status and, therefore, fT4 may be in the future, it will become an indicator to measure whether the thyroid function of animals in the acute phase is normal. More importantly, these phenomena observed in animal patients are consistent with the recovery patterns of patients with severe NTIS observed in human medicine. They represent a high probability of future human-related research on NTIS, which can be applied to animals.

► **Figure 2** Box-and-Whisker plots of the serum total thyroxine(tT4) concentrations (nmol/L) at the 4 major study time points. The shaded area indicates the reference interval.

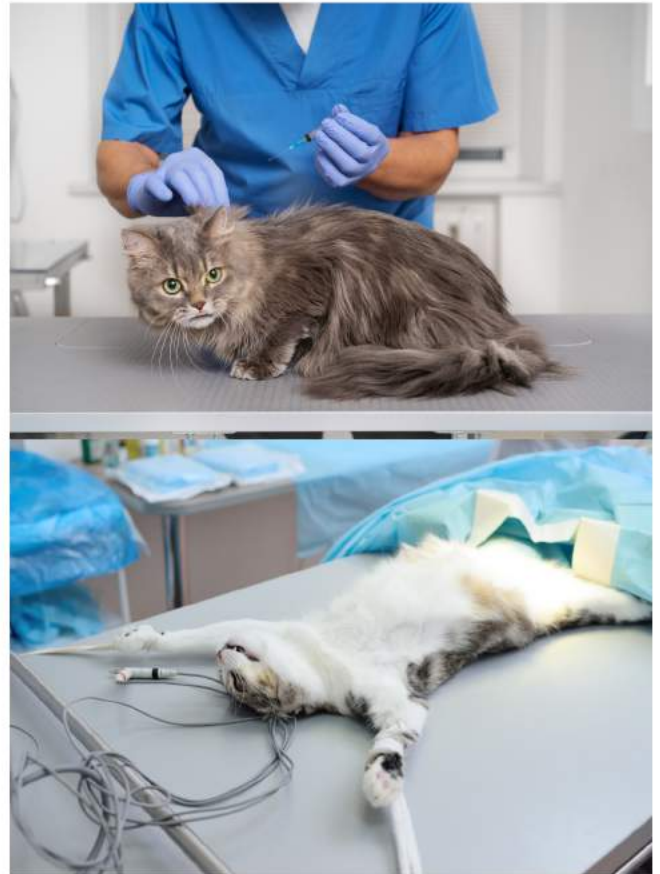


**Note:** The red line is the line segment connecting the median serum tT4 concentrations at the 4 major study time points. It can be seen that the tT4 concentration gradually tends to normal. The Box-and-Whisker plots are from "Thyroid function tests during nonthyroidal illness syndrome and recovery in acutely ill dogs", by Timothy A. Bolton, David L. Panciera, Caylie D. Voudren, Matthew I. Crawford-Jennings, 2023, Journal of Veterinary Internal Medicine, 2024 Jan-Feb;38(1), p.115.

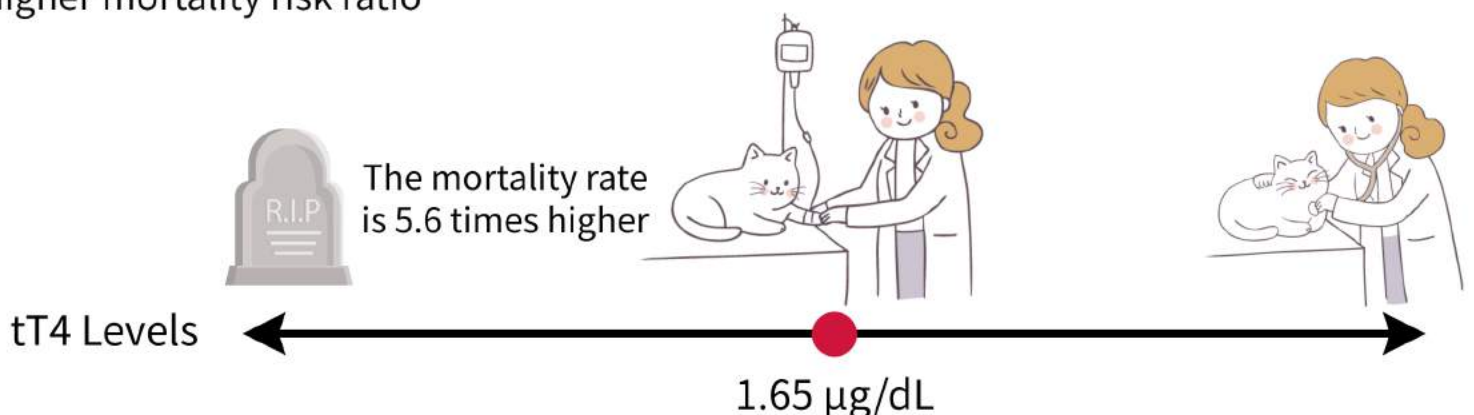


## Research on Cats with NTIS: The tT4 Concentration among Cats with NTIS Is Also Low, and Its tT4 Concentration Is Highly Correlated with Disease Severity and Mortality

In a 2021 Veterinary sciences study on cats, tT4 concentrations in acutely ill hospitalized cats were studied and compared with a group of non-hospitalized cats with NTIS (chronic disease group). In comparison to T3 and TSH, tT4 was chosen because of its availability and ease of testing. Results: In the critically ill cat group, it was observed that the tT4 concentration of this group was lower than that of the chronic disease group, which is consistent with the observations in humans and canine patients. The results of this study show that the lower the tT4, the worse the prognosis and the higher the mortality rate. The measured tT4 concentration of  $1.65 \mu\text{g/dL}$  is considered to be used as a predictor of mortality in critically ill cats ( $p = 0.04$ ), because acutely severe hospitalized cats with tT4 less than  $1.65 \mu\text{g/dL}$  have a mortality risk ratio greater than  $1.65 \mu\text{g/dL}$ . Mortality cases are 5.6 times higher.



► **Figure 3** Acutely severe hospitalized cats with tT4 level less than  $1.65 \mu\text{g/dL}$  have a higher mortality risk ratio





From the above information, we know that NTIS may occur in critically ill animals. When veterinarians suspect that the disease has thyroid problems and is mixed with other acute diseases, tT4 can be detected. Its measured value can be used to evaluate the animal's survival probability and prognosis. After the acute illness is relieved (2 to 4 weeks after discharge), tT4 testing and tracking must be performed again to avoid misdiagnosing the source of the disease due to the influence of NTIS. It is clinically important to track and detect tT4 during the early, middle, and late stages of treatment.



#### ◆ Reference

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