

Differentiating Graves disease from Hashitoxicosis in children: Clinical and biochemical predictors

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ABSTRACT

Objective: Differentiating Graves disease (GD) from Hashitoxicosis in children is often challenging due to overlapping clinical and biochemical features at presentation. This study aimed to evaluate the diagnostic utility of commonly available clinical and biochemical parameters to support etiologic classification in pediatric autoimmune thyrotoxicosis.

Materials and Methods: We retrospectively analyzed 58 children aged 0–18 years diagnosed with autoimmune thyrotoxicosis between 2019 and 2025. Clinical, laboratory, and imaging findings were compared between patients with GD and Hashitoxicosis. Receiver operating characteristic (ROC) analysis and logistic regression were performed to assess the diagnostic performance of key parameters.

Results: The cohort was female-predominant, with similar sex distribution between groups (34/44, 77.3% in GD vs 11/14, 78.6% in Hashitoxicosis). Palpitations were the most common presenting symptom (17, 29.3 %). Incidental detection occurred in 17 (29.3%), of whom 9 (52.9%) had subtle symptoms identified on detailed clinical evaluation. Ophthalmopathy was observed exclusively in GD (13, 29.5%). fT3 levels and the fT3/fT4 ratio were significantly higher in GD than in Hashitoxicosis ($p = 0.002$ and $p = 0.001$, respectively). TRAb showed the highest diagnostic performance (AUC = 0.950), followed by fT3 (AUC = 0.856) and the fT3/fT4 ratio (AUC = 0.809). A TRAb cut-off of 2.6 IU/L yielded 75% sensitivity and 100% specificity, whereas fT3 ≥ 6 pg/mL yielded 93% sensitivity and 46% specificity. Anti-TPO and anti-Tg antibodies showed poor discriminatory value. TRAb remained independently associated with GD (OR = 3.61, $p = 0.011$). Nine children with Hashitoxicosis (64.3%) were managed without treatment and achieved spontaneous resolution.

Conclusion: Differentiating GD from Hashitoxicosis requires an integrated assessment of clinical features, antibody status, and hormone dynamics. TRAb remains the most informative marker, while fT3 and the fT3/fT4 ratio may provide complementary value. Anti-thyroid antibodies have limited utility for etiologic differentiation. Accurate classification helps guide the management and avoid unnecessary treatment.

Keywords: Autoimmune, Graves disease, hyperthyroidism, thyroiditis

Introduction

Autoimmune thyrotoxicosis is a rare but clinically significant endocrine disorder in childhood, most commonly caused by Graves disease (GD) and, less frequently, by Hashitoxicosis, the transient thyrotoxic phase of Hashimoto thyroiditis (1–4). Differentiating between these two etiologies is clinically important, as their natural history, treatment strategies, and long-term prognosis differ substantially. While GD typically requires prolonged antithyroid drug (ATD) therapy, Hashitoxicosis is generally self-limiting and may not require pharmacological intervention (5–7).

The diagnosis of autoimmune thyrotoxicosis in children is primarily based on clinical findings, thyroid function tests, and thyroid autoantibodies. However, overlapping features between GD and Hashitoxicosis—such as suppressed thyroid-stimulating

hormone (TSH) levels and elevated thyroid hormones—can complicate early etiological differentiation (5,6,8). Various diagnostic tools, including TSH receptor antibodies (TRAb) and imaging findings such as increased thyroid vascularity or diffusely increased radionuclide uptake, have been proposed to aid in distinguishing these entities (2).

Despite the availability of these diagnostic approaches, pediatric data evaluating their relative diagnostic performance remain limited, and early etiologic differentiation in routine clinical practice often relies on clinical judgment rather than standardized criteria.

Therefore, this study aimed to evaluate the diagnostic performance of commonly used clinical and biochemical parameters, particularly TRAb and thyroid hormone levels, to support early etiologic classification and guide treatment decisions in children with autoimmune thyrotoxicosis.

Materials and Methods

Study design and participants

This retrospective study was conducted at the Pediatric Endocrinology Department of Kocaeli City Hospital and included children and adolescents aged <18 years diagnosed with autoimmune thyrotoxicosis between January 2019 and October 2025. Patients were identified from institutional electronic records using ICD codes for hyperthyroidism and autoimmune thyroid disorders.

Patient selection and classification

Patients with suppressed TSH and elevated fT3 and/or fT4 were screened. Inclusion criteria were (1) age <18 years, (2) biochemical thyrotoxicosis (suppressed TSH with elevated fT3 and/or fT4), (3) confirmed autoimmune etiology based on antibody profile and/or imaging findings, and (4) availability of sufficient clinical and follow-up data to allow definitive classification.

GD was diagnosed by suppressed TSH with elevated fT3 and/or fT4 together with positive TRAb. Increased thyroid vascularity on Doppler ultrasonography, ophthalmopathy, and/or scintigraphic findings were used as supportive features in cases with inconclusive serology, consistent with current guidelines recommending antibody-based diagnosis and selective use of imaging (9,10).

In TRAb-negative patients, GD was diagnosed based on typical clinical features of thyrotoxicosis, diffuse goiter, supportive ultrasonographic findings (increased vascularity), and/or diffusely increased uptake on scintigraphy when available. Clinical course and response to antithyroid treatment further supported the diagnosis.

Hashitoxicosis was defined as a form of destructive thyrotoxicosis associated with autoimmune thyroiditis and was diagnosed in patients with positive anti-TPO and/or anti-Tg antibodies, negative or borderline TRAb levels, and a transient thyrotoxic course.

Subacute thyroiditis was excluded based on clinical findings (thyroid pain or tenderness), inflammatory markers and ultrasonographic features. Nodular etiologies were excluded by ultrasonography and, when necessary, further assessed by scintigraphy to rule out toxic nodular disease or autonomous functioning nodules.

The distinction between Graves disease and Hashitoxicosis was based on the presence of TRAb and clinical course, distinguishing antibody-mediated hyperthyroidism from destructive thyrotoxicosis.

A total of 80 patients presenting with biochemical thyrotoxicosis were screened during the study period. After exclusion of 22 patients based on predefined criteria, including subclinical hyperthyroidism (n=7), drug-induced thyrotoxicosis (n=3), toxic adenoma (n=2), subacute thyroiditis (n=4), and incomplete clinical data or follow-up shorter than three months (n=6), 58 patients with confirmed autoimmune thyrotoxicosis were included in the final analysis. The screening process and reasons for exclusion are summarized in a flow diagram (Figure 1).

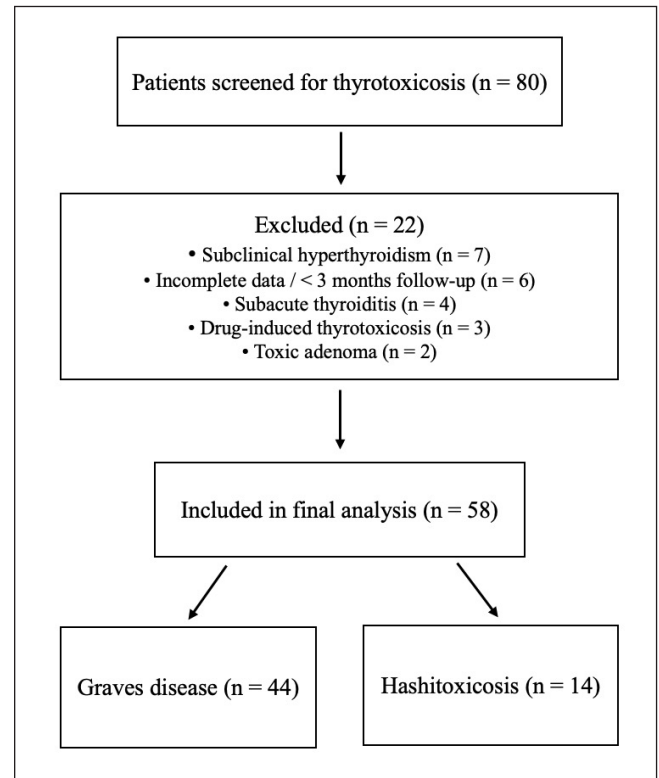


Figure 1: Flow diagram of patient selection and classification.

Data collection, laboratory analyses and imaging

At presentation, demographic characteristics, symptoms, physical findings, Tanner stage, family history, and anthropometric measurements were recorded. Weight, height, and body mass index (BMI) standard deviation scores (SDS) were calculated using Turkish reference standards (11). Goiter was graded according to WHO criteria as grade 0 (absent), grade 1 (palpable but not visible), or grade 2 (visible) (12). Ophthalmopathy was defined as the presence of lid lag, lid retraction, or proptosis on physical examination (13). Serum fT3, fT4, TSH, anti-TPO, and anti-Tg were measured by chemiluminescent immunoassay, and TRAb by a third-generation binding immunoassay. The institutional laboratory reference ranges were 2.5–5.2 pg/mL for fT3, 0.9–1.6 ng/dL for fT4, 0.6–4.9 µIU/mL for TSH, 0–35 IU/mL for anti-TPO, 0–120 IU/mL for anti-Tg, and 0.1–2 IU/L for TRAb. Positivity was defined as values exceeding the upper limit of the reference range; accordingly, TRAb values >2 IU/L were considered positive. Thyroid ultrasonography with Doppler was performed in all patients to assess echotexture, vascularity, gland volume, and nodules. Vascularity was evaluated qualitatively based on diffuse hypervascularity on color Doppler, and gland volume was calculated using the ellipsoid formula and interpreted according to age- and gender-specific reference values (14). Scintigraphy was performed selectively in diagnostically uncertain cases; diffuse homogeneous uptake supported GD. Imaging findings were not used in isolation for diagnosis, in line with current guidelines (9,10).

Treatment and follow-up

All patients with GD received methimazole at an initial dose of 0.2–0.5 mg/kg/day, with doses up to 1.0 mg/kg/day (maximum

30 mg/day) reserved for severe thyrotoxicosis and subsequently adjusted to the lowest effective dose. Treatment was continued for a minimum of 2 years, and discontinuation was considered in patients who sustained euthyroidism for at least 6–12 months on a minimal maintenance dose (2.5–5 mg/day), in line with guideline-based practice. Beta-blockers (e.g., propranolol) were initiated at diagnosis in patients with significant adrenergic symptoms, such as tachycardia, tremor, and palpitations, and were tapered as symptoms improved. Hashitoxicosis was managed conservatively; β -blockers were used only for symptomatic relief, and no patient received antithyroid drugs. Patients were followed every 4–6 weeks initially and every 3–6 months once stable. Euthyroidism was defined as normalization of fT3 and/or fT4 levels, regardless of TSH status. Remission was defined as sustained euthyroidism for at least 12 months following ATD withdrawal, whereas relapse was defined as recurrence of biochemical hyperthyroidism after at least 12 months of ATD therapy and subsequent discontinuation. Adverse effects related to MMI (e.g., rash, hepatic dysfunction, neutropenia) and any dose modifications were documented throughout follow-up. Patients classified as Hashitoxicosis were required to demonstrate a transient thyrotoxic course with spontaneous resolution during follow-up, ensuring diagnostic confirmation and stability without the need for reclassification.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 26.0. Continuous variables were presented as median (interquartile range), and categorical variables as frequencies and percentages. Normality was assessed using the Shapiro–Wilk test. Between-group comparisons of continuous variables were performed using the Mann–Whitney U test, while categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) analysis was used to evaluate diagnostic performance; areas under the curve (AUCs) with 95% confidence intervals were calculated, and optimal cutoff values were determined using the Youden index. Binary logistic regression was performed to identify independent predictors of Graves disease, with model fit assessed using the Hosmer–Lemeshow test and Nagelkerke R^2 . Spearman correlation analysis and multivariable linear regression were used to evaluate associations with time to euthyroidism. A two-sided p value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 58 pediatric patients with hyperthyroidism were included, comprising 44 (75.9%) with GD and 14 (24.1%) with Hashitoxicosis. The median age at diagnosis was 15.3 years (13.2–16.7), and 45 (77.6%) were female. Anthropometric characteristics, including weight, height, BMI, and thyroid volume SDS, were comparable between the groups, with no statistically significant differences (Table I).

The most common presentations were palpitations (17, 29.3%) and incidentally detected low TSH (17, 29.3%), followed by neck swelling (6, 10.3%) and weight loss (6, 10.3%). Palpitations

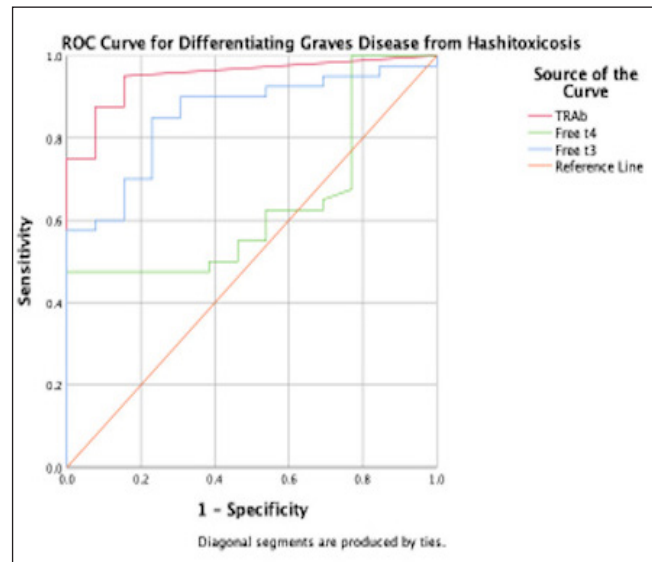


Figure 2: ROC curves of diagnostic markers for differentiating Graves disease and Hashitoxicosis.

(14, 31.8% vs 3, 21.4%) and weight loss (5, 11.4% vs 1, 7.1%) were more frequent in GD ($p=0.030$ and $p=0.040$), while tremor occurred exclusively in GD (3, 7.1%; $p=0.009$). Among 17 (29%) initially asymptomatic patients, detailed evaluation identified palpitations in 5 (29.4%), weight loss in 3 (17.6%), irritability in 2 (11.8%), and tachycardia in 8 (47.1%). Overall, goiter was observed in 42 (72.4%) patients, with no significant difference between the GD and Hashitoxicosis groups (70.5% vs 78.6%, $p=0.550$). Ophthalmopathy was observed in 13 (29.5%) and occurred exclusively in the GD group ($p=0.030$). A family history of thyroid disease was present in 33 (56.9%), most commonly hypothyroidism (17, 29.3%), followed by GD and thyroid nodules (7, 12.1% each), with no group difference ($p=0.980$). Comorbid autoimmune disease occurred in 3 (5.1%), all with GD (type 1 diabetes, $n=2$; vitiligo, $n=1$; $p=0.39$). Thyroid nodules were found in 8 (13.8%), with no group difference ($p=0.42$).

Laboratory and imaging findings

At diagnosis, serum TSH levels were markedly suppressed in all patients. Thyroid autoantibody positivity was observed in 52 (89.7%), including anti-TPO alone in 13 (22.4%), anti-Tg alone in 11 (19.0%), and both antibodies in 28 (48.3%), while 6 (10.3%) were negative for both antibodies.

Median fT3 levels were significantly higher in Graves disease than in Hashitoxicosis (10.00 [7.13–16.80] vs 6.27 [5.66–6.98] pg/mL, $p=0.002$), whereas median fT4 levels did not differ significantly between groups (2.95 [2.30–5.67] vs 2.76 [2.17–3.01] ng/dL, $p=0.098$). The fT3/fT4 ratio was significantly higher in patients with GD compared with those with Hashitoxicosis (median 3.27 [2.50–4.50] vs 2.20 [1.80–3.10], $p=0.001$). TRAb levels were significantly higher in the GD group (4.10 [2.36–12.70] vs 0.10 [0.10–0.10] IU/L, $p<0.001$). In contrast, anti-TPO and anti-Tg titers did not differ significantly between groups ($p=0.347$ and $p=0.748$, respectively) (Table II).

Treatment and follow-up

Methimazole (MMI) therapy was initiated in all patients with GD, with a median starting dose of 0.29 mg/kg/day (0.20–

Table I: Clinical, laboratory, and treatment characteristics of patients with Graves disease and Hashitoxicosis

Variable	Graves 44 (75.9)	Hashitoxicosis 14 (24.1)	Total (58)	p
Total number of patients*	44 (75.9)	14 (24.1)	58	
Age, years [†]	15.36 (13.27–16.74)	15.25 (13.12–17.30)	15.30 (13.20–16.70)	0.820
Female gender [*]	34 (77.3)	11 (78.6)	45 (77.6)	0.910
Weight SDS [†]	-0.50 (-1.25–0.80)	0.10 (-1.82–1.50)	-0.50 (-1.30–1.00)	0.180
Height SDS [†]	-0.20 (-0.79–0.80)	0.30 (-0.81–0.82)	-0.10 (-0.80–0.80)	0.270
BMI SDS [†]	0.07 (-1.10–0.90)	0.20 (-1.51–1.77)	0.10 (-1.20–1.00)	0.310
Reason for presentation [*]				
Palpitations	14 (31.8)	3 (21.4)	17 (29.3)	0.030
Low TSH detected incidentally	11 (25.0)	6 (42.9)	17 (29.3)	0.420
Weight loss	5 (11.4)	1 (7.1)	6 (10.3)	0.040
Tremor	3 (7.1)	0 (0)	3 (5.1)	0.009
Fatigue	2 (4.8)	2 (14.3)	4 (6.8)	0.380
Neck swelling	4 (9.1)	2 (14.3)	6 (10.3)	0.060
Goiter	31 (70.5)	11 (78.6)	42 (72.4)	0.550
Grade 1	10 (22.7)	3 (21.4)	13 (22.4)	
Grade 2	21 (47.7)	8 (57.1)	29 (50.0)	
Ophthalmopathy	13 (29.5)	0 (0)	13 (22.4)	0.030
Family history of thyroid disease	25 (56.8)	8 (57.1)	33 (56.9)	0.980
Comorbidity	3 (6.8)	0 (0)	3 (5.1)	0.390
Thyroid nodule	7 (15.9)	1 (7.1)	8 (13.8)	0.420
Thyroid volume SDS [†]	3.50 (1.85–7.80)	3.02 (1.84–7.68)	3.56 (1.86–7.89)	0.470

*: n(%) (Fisher's exact test), †: median (n(%) (interquartile range) (Mann-Whitney U test), **SDS**: standard deviation score, **BMI**: body mass index

Table II: Comparison of laboratory parameters between Graves disease and Hashitoxicosis

Parameter	Graves Disease*	Hashitoxicosis*	p
fT3 (pg/mL)	10.00 (7.13–16.80)	6.27 (5.66–6.98)	0.002
fT4 (ng/dL)	2.95 (2.30–5.67)	2.76 (2.17–3.01)	0.098
fT3/fT4 ratio	3.27 (2.50–4.50)	2.20 (1.80–3.10)	0.001
TRAb (IU/L)	4.10 (2.36–12.70)	0.10 (0.10–0.10)	< 0.001
Anti-TPO (IU/mL)	198 (56.9–556)	150 (30–311)	0.347
Anti-Tg (IU/mL)	98 (33–420)	308 (151–388)	0.748

*: median (interquartile range) (Mann-Whitney U test), **fT3**: free triiodothyronine, **fT4**: free thyroxine, **TRAb**: thyrotropin receptor antibody, **anti-TPO**: anti-thyroid peroxidase antibody, **anti-Tg**: anti-thyroglobulin antibody

0.60), whereas none of the patients with Hashitoxicosis received antithyroid treatment.

Beta-blocker therapy was prescribed in 31 (70.5%) with GD and 5 (35.7%) with Hashitoxicosis. Combined MMI and beta-blocker therapy was used in 31 (70.5%) with GD, whereas 9 (64.3%) with Hashitoxicosis required no pharmacologic treatment.

Median time to euthyroidism was 7.0 weeks with MMI alone and 8.0 weeks with combination therapy ($p = 0.606$). Overall, time to euthyroidism was 7 (5–12) weeks in GD and 8 (8–13) weeks in Hashitoxicosis; median follow-up was 15 (8–36) and 13 (9–30) months, respectively.

Subgroup analyses

Graves disease subgroup

Among the 44 with GD, 34 (77.3%) were female. The most frequent presenting features were palpitations (14, 31.8%) and incidentally detected low TSH levels (11, 25.0%). TRAb positivity was present in 42 (95.5%), among the two TRAb-negative cases, one showed positivity for both anti-TPO and anti-Tg antibodies, while the other was positive for anti-TPO alone.

Isolated anti-TPO positivity was rare (3, 7.1%), whereas

isolated anti-Tg positivity was more frequent (18, 42.9%), and combined anti-TPO and anti-Tg positivity was observed in 21 (50.0%). Thyroid scintigraphy was performed in 12 (27.3%) and demonstrated diffusely increased uptake in all patients. Two patients (4.5%) experienced hematologic adverse effects due to MMI treatment. One developed transient neutropenia during the first month of treatment; MMI was temporarily replaced with propylthiouracil and later reintroduced at a lower dose without recurrence. The second patient developed pancytopenia after 21 months of MMI therapy, necessitating definitive surgical treatment. No hepatic toxicity or cutaneous adverse reactions were observed. Hospitalization was required in 4 patients (9.1%), primarily due to severe thyrotoxicosis, treatment non-compliance, or adverse drug reactions.

Three patients discontinued MMI therapy after 12, 17, and 30 months, respectively. The patient who discontinued at 30 months experienced relapse six months later, whereas the other two remained euthyroid at the last follow-up.

Hashitoxicosis subgroup

Among the 14 cases, the most frequent presentation was incidental biochemical abnormality (6, 42.9%), and none exhibited ophthalmopathy. All cases with Hashitoxicosis showed positivity for at least one thyroid autoantibody; isolated anti-TPO positivity was uncommon (1, 7.1%), isolated anti-Tg positivity was observed in 6 (42.9%), and combined anti-TPO and anti-Tg positivity was present in 7 (50.0%). All were TRAb-negative according to the institutional laboratory reference range except for one case with a mildly elevated TRAb level (2.4 IU/L) at presentation; this normalized during follow-up, consistent with a transient course of thyrotoxicosis.

Nine (64.3%) were followed without medication. In this untreated subgroup, median baseline fT4 and fT3 levels were 2.95 ng/dL (1.84–3.17) and 6.55 pg/mL (3.15–8.40), respectively, and all achieved spontaneous normalization of thyroid function during

Table III: Diagnostic accuracy of biomarkers for differentiating Graves disease from Hashitoxicosis

Variable	AUC (95% CI)	p	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TRAb (TSI)	0.950 (0.89–0.99)	<0.001	2.6 IU/L	75	100	100.0	56.0
fT3	0.856 (0.75–0.96)	<0.001	6.0 pg/mL	93	46	84.4	67.6
fT3/fT4 ratio	0.809 (0.67–0.95)	0.001	2.84	77	85	94.2	54.0
fT4	0.641 (0.48–0.80)	0.129	—	—	—	—	—
Anti-TPO	0.534	0.167	—	—	—	—	—
Anti-Tg	0.459	0.138	—	—	—	—	—

AUC: Area under the receiver operating characteristic curve, **CI:** Confidence interval, **PPV:** Positive predictive value, **NPV:** Negative predictive value, **TRAb:** Thyrotropin receptor antibody

Table IV: Logistic regression analysis of predictors of Graves disease

Variable	Univariable OR (95% CI)	p	Multivariable B	Adjusted OR (95% CI)	p
TRAb (TSI)	2.78 (1.50–5.15)	<0.001	1.28	3.61 (1.35–9.65)	0.011
fT3/fT4 ratio	1.54 (1.10–2.15)	0.001	0.42	1.52 (0.68–3.40)	0.302

Model Statistics: The multivariable model was statistically significant, $\chi^2(2) = 33.93$, $p < 0.001$; Nagelkerke $R^2 = 0.704$; Hosmer–Lemeshow $p = 0.906$; overall correct classification = 88.7%. **OR:** Odds ratio, **CI:** Confidence interval, **TRAb:** Thyrotropin receptor antibody, **fT3:** Free triiodothyronine, **fT4:** Free thyroxine.

follow-up.

Five patients (35.7%) required L-thyroxine replacement during follow-up, initiated between one and three months after diagnosis. No relapses, hospitalizations, or drug-related adverse events were observed in this subgroup.

Diagnostic accuracy analyses

TRAb exhibited the highest diagnostic accuracy for distinguishing GD from Hashitoxicosis, showing an outstanding AUC of 0.950 (95% CI 0.89–0.99, $p < 0.001$). This was followed by fT3 levels and the fT3/fT4 ratio, which demonstrated robust discriminatory performance with AUC values of 0.856 (95% CI 0.75–0.96, $p < 0.001$) and 0.809 (95% CI 0.67–0.95, $p = 0.001$), respectively (Figure 2). A TRAb cutoff value of 2.6 IU/L yielded a sensitivity of 75% and a specificity of 100%. In comparison, an fT3 cutoff 6.0 pg/mL was associated with a sensitivity of 93% and a specificity of 46%. In contrast, fT4 did not demonstrate statistically significant discriminatory performance (AUC=0.641, 95% CI 0.48–0.80, $p = 0.129$). Similarly, anti-TPO and anti-Tg showed poor discriminatory ability, with AUC values of 0.534 and 0.459, respectively ($p > 0.05$ for both) (Table III).

The fT3/fT4 ratio also demonstrated robust discriminatory performance, showing an AUC of 0.809 (95% CI 0.67–0.95, $p = 0.001$). A cutoff value of 2.84 yielded a sensitivity of 77% and a specificity of 85%.

Binary logistic regression analysis was performed including TRAb and the fT3/fT4 ratio as candidate variables. The overall model was statistically significant ($\chi^2 = 33.93$, $p < 0.001$) and demonstrated good explanatory power (Nagelkerke $R^2 = 0.704$). Model fit was acceptable according to the Hosmer–Lemeshow test ($p = 0.906$).

In the multivariable model, TRAb remained independently associated with Graves disease ($p = 0.011$), with each one-unit increase associated with a 3.6-fold higher odds of Graves disease (OR = 3.61, 95% CI 1.35–9.65) (Table IV).

Although the fT3/fT4 ratio was significantly higher in Graves disease and demonstrated good diagnostic performance in ROC analysis, it did not retain statistical significance in the multivariable model ($p = 0.302$).

Correlation and predictive modeling

Spearman's rank correlation analysis demonstrated that TRAb levels were positively correlated with both fT4 ($r = 0.459$, $p < 0.001$) and fT3 ($r = 0.598$, $p < 0.001$), indicating that greater autoimmune stimulation was associated with more severe biochemical thyrotoxicosis. Consistently, the initial methimazole dose showed positive correlations with baseline fT4 ($r = 0.334$, $p = 0.019$), fT3 ($r = 0.338$, $p = 0.019$), and TRAb ($r = 0.424$, $p = 0.004$), suggesting that treatment intensity reflected disease severity at presentation.

Within the GD group, no significant correlation was observed between TRAb levels and the fT3/fT4 ratio ($r = 0.049$, $p = 0.766$).

Time to achieve euthyroidism was positively correlated with baseline fT3 ($r = 0.307$, $p = 0.021$) and TRAb ($r = 0.288$, $p = 0.035$), but not with fT4 ($p = 0.143$). These findings indicate that higher initial fT3 and TRAb levels were associated with a longer duration to biochemical normalization.

Discussion

This study shows that although GD and Hashitoxicosis share overlapping clinical and biochemical features, an integrated diagnostic approach can improve etiologic classification and help avoid unnecessary antithyroid treatment. TRAb remains the most potent independent predictor of GD, yet the fT3/fT4 ratio and fT3 levels provide crucial complementary value, particularly in cases where serology may be delayed or borderline. Importantly, nearly two-thirds of children with Hashitoxicosis achieved spontaneous resolution without pharmacological treatment, underscoring the importance of accurate early classification.

In our cohort, Hashitoxicosis accounted for nearly one-quarter of pediatric autoimmune thyrotoxicosis patients. Reported prevalence in pediatric studies varies widely (0.5–22%), likely reflecting differences in diagnostic criteria, study design, and referral patterns (5,6,8). Similar rates have been reported in cohorts from Turkey and Scotland (approximately 15% and 19.6%, respectively) (1,15). Hashitoxicosis represents a clinically meaningful proportion of pediatric thyrotoxicosis, warranting consideration during the initial evaluation.

Both conditions predominantly affected adolescent females, with no significant differences in age or sex distribution, consistent with previous reports (9,10,16). Despite similar demographic characteristics, the clinical presentation was heterogeneous and often subtle. Palpitations, weight loss, and tremor were common presenting features, while incidental detection occurred more frequently than previously reported in pediatric cohorts (42.9% in Hashitoxicosis and 25.0% in GD vs. 3.9–4.5%) (2,3,5,17). Closer evaluation revealed subtle symptoms in many initially asymptomatic patients, suggesting that pediatric thyrotoxicosis may be under-recognized when overt symptoms are absent.

Ophthalmopathy provides a clinically meaningful point of distinction between Graves disease and Hashitoxicosis. Previous pediatric studies report ophthalmopathy in approximately 25–50% of children with GD, whereas it is distinctly uncommon in Hashimoto thyroiditis, occurring in approximately 2% of cases (18,19). In line with this pattern, ophthalmopathy in our cohort was observed exclusively in Graves disease, affecting 29.5% of patients. These findings support ophthalmopathy as a practical clinical marker for distinguishing GD from Hashitoxicosis.

In this setting, elevated free T3 levels and the fT3/fT4 ratio may provide useful diagnostic clues. T3-predominant hyperthyroidism is more characteristic of Graves disease, as consistently reported in pediatric studies (9,10,20). In line with this, a cohort of 105 children demonstrated that median free T3 levels at diagnosis were markedly higher in Graves disease compared to Hashitoxicosis (15.2 vs. 7.0 pg/mL), supporting the diagnostic relevance of this pattern (21). In our cohort, a free T3 threshold of 6 pg/mL showed high sensitivity of 93% but limited specificity of 46% for Graves disease, indicating that free T3 may be useful as an initial indicator but lacks sufficient specificity for standalone diagnostic use. Building on this, the fT3/fT4 ratio demonstrated stronger diagnostic performance than previously reported pediatric data, suggesting that relative T3 predominance, rather than absolute hormone levels alone, provides more robust discriminatory value (21). Its lack of correlation with TRAb suggests that the two markers reflect different aspects of disease physiology, making the fT3/fT4 ratio a useful adjunct when TRAb results are delayed or equivocal.

Given these considerations, additional biochemical markers may provide complementary diagnostic value. TRAb remains a key diagnostic tool in pediatric thyrotoxicosis and is typically positive in Graves disease while absent in Hashitoxicosis, as reflected in current guidelines (2,10,22). However, a small subset of children may initially be TRAb-negative despite overt hyperthyroidism, with some later demonstrating seroconversion, indicating that TRAb negativity does not entirely exclude GD (23,24). Conversely, although rare, TRAb positivity has been reported in approximately 5% of patients with autoimmune thyroiditis (21). In our study, TRAb positivity was incorporated into the diagnostic classification, reflecting routine clinical practice. Its diagnostic performance should be interpreted cautiously because incorporation bias may have led to overestimation. TRAb may therefore be better viewed as a classification-linked marker rather than a fully independent predictor, and its optimal cutoff may vary across assays.

In contrast, anti-TPO and anti-Tg antibodies showed limited clinical utility for etiologic differentiation. While thyroid

autoantibodies are essential markers of autoimmune thyroid disease, they showed limited discriminatory value in this cohort in differentiating Graves disease from Hashitoxicosis in children (2,20,25). Previous studies describe these antibodies as non-specific markers that may be elevated in both conditions during hyperthyroid phases in childhood (5). Their poor diagnostic performance and substantial individual overlap limit their usefulness for routine etiologic differentiation.

All patients with Graves disease in our cohort required antithyroid drug therapy, with the majority also receiving β -blockers for symptomatic control and only 4.5% experiencing clinically significant adverse events, including one case requiring thyroidectomy. This pattern is consistent with previous pediatric studies indicating that Graves disease typically necessitates prompt initiation of active treatment, with methimazole as the first-line agent despite reported adverse effects in up to 20–30% of patients and rare serious complications (<1%) (9,10,26–28).

In contrast, Hashitoxicosis is often managed conservatively, with pharmacological treatment reserved for symptomatic patients; consistent with pediatric series reporting β -blocker use in 8–29% of patients and rare need for antithyroid drugs (1,6,8), in our cohort β -blockers were administered only to symptomatic patients (35.7%), and no patients received antithyroid therapy. Given these differences in treatment, early etiologic differentiation is important for appropriate management. Pediatric thyrotoxicosis generally resolves within weeks to months, although the time course varies by etiology and disease severity, with most children achieving biochemical normalization within the first 4–12 weeks (6,8,26,28,29). In our cohort, although time to euthyroidism was comparable between etiologies, its association with higher baseline fT3 and TRAb levels suggests that greater biochemical and autoimmune activity at presentation may be linked to a slower recovery.

Limitations

The main limitations of this study are its retrospective, single-center design, the relatively small number of patients with Hashitoxicosis, and incomplete availability of some diagnostic data. Because TRAb was incorporated into the diagnostic classification, its diagnostic performance may have been overestimated. Thyroid vascularity was assessed qualitatively rather than quantitatively, and long-term remission and relapse outcomes were not systematically evaluated.

Conclusion

Differentiating Graves disease from Hashitoxicosis in children remains challenging, particularly at initial presentation. Our findings suggest that no single parameter is sufficient for reliable etiologic classification; instead, combining clinical features, antibody status, and hormone dynamics offers a more comprehensive approach. TRAb remains the key diagnostic marker, with fT3 and the fT3/fT4 ratio providing additional support, whereas anti-TPO and anti-Tg offer limited discriminatory value. Accurate classification is clinically important, as many children with Hashitoxicosis may recover without antithyroid therapy, allowing treatment to be tailored more appropriately.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kocaeli City Hospital (December 27, 2025, reference number: 2025-15).

Contribution of the authors

Study conception and design: SHK; data collection: SHK, FK, ES; statistical analysis: SHK, NÖM; interpretation of results: SHK, FK; manuscript drafting and critical revision: SHK, FK. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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