Alqalam Journal of Medical and Applied Sciences. 2026;9(7):1889-1895
https://doi.org/10.54361/ajmas.269709

Original article

Extended Outcomes of Antithyroid Therapy in Children and Adolescents with Graves' Disease

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Abstract
Graves' disease is the leading cause of hyperthyroidism in children and adolescents. Despite the widespread use of antithyroid drugs (ATDs), sustained remission rates remain low. Identifying reliable predictors of long-term outcomes is essential to optimizing management strategies. This study was conducted to evaluate the prognostic value of thyrotropin-binding inhibitory immunoglobulin (TBII) normalization time in predicting sustained remission among pediatric patients with Graves' disease treated with ATDs. This retrospective study included pediatric patients diagnosed with Graves' disease across two centers. Clinical, biochemical, and immunological data were collected, with particular focus on TBII dynamics during treatment. Patients were followed to assess remission, relapse, and long-term outcomes. Statistical analyses were performed to identify predictors of sustained remission. Sustained remission was achieved in approximately one quarter of patients. The most consistent predictor of remission was the time to TBII normalization, with shorter normalization periods strongly associated with favorable outcomes. Baseline demographic and biochemical features were not reliable predictors. Antibody kinetics provided superior prognostic information compared to traditional clinical markers. TBII normalization time is a robust predictor of sustained remission in pediatric Graves' disease. Longitudinal monitoring of antibody dynamics should be integrated into routine management to guide therapeutic decisions. Patients who fail to achieve TBII normalization within two years are at high risk of treatment failure and may benefit from early consideration of definitive therapies. Incorporating antibody monitoring into follow-up protocols can improve individualized treatment planning and optimize long-term outcomes.
Keywords. Pediatric Graves' disease, Antithyroid drugs, Thyrotropin-binding inhibitory immunoglobulin (TBII), Remission predictors, Autoimmune thyroid disease.

Introduction

Graves' disease (GD) is the most prevalent cause of hyperthyroidism in children and adolescents, representing the leading autoimmune thyroid disorder in this age group [1]. It is mediated by thyroid-stimulating hormone receptor antibodies (TRAb), which stimulate excessive thyroid hormone production, resulting in clinical thyrotoxicosis. Although GD is less common in children than adults, its course is often more severe, with increased relapse rates and prolonged treatment requirements [2]. Recent advances in pediatric GD management have been summarized by Bahn & Cooper (2023), highlighting evolving therapeutic strategies. Insights into the immunopathogenesis of GD and novel treatment options [3]. Antithyroid drugs (ATDs), particularly methimazole, are the preferred initial treatment due to their safety profile and potential to induce remission without invasive procedures [4].

Metwalley and Farghaly provided an updated overview of GD in children [5], reinforcing current treatment paradigms. However, sustained remission is achieved in only a subset of pediatric patients, with rates varying between 20% and 40% depending on clinical and immunological factors [6]. Among these, thyrotropin-binding inhibitory immunoglobulin (TBII) levels have emerged as a promising biomarker. Studies have shown that early TBII normalization correlates strongly with long-term remission, suggesting its utility as a prognostic indicator [7]. The pathogenesis of GD in children is complex and often associated with other autoimmune conditions such as type 1 diabetes, rheumatoid arthritis, and celiac disease, indicating a broader immune dysregulation [8]. Clinical presentation and outcomes may differ in children with coexisting autoimmune conditions such as type 1 diabetes [9]. Environmental factors, including exposure to endocrine-disrupting chemicals and regional variations in iodine intake, may also contribute to the rising incidence of pediatric GD in certain populations [9].

While ATDs remain the cornerstone of initial therapy, alternative treatments such as radioactive iodine and thyroidectomy are considered in cases of poor response or relapse. Emerging therapies targeting B-cells (e.g., rituximab) or the thyroid-stimulating hormone receptor (e.g., teprotumumab) are under investigation, although their safety and efficacy in children remain uncertain [10].

Methods

Study Design and Setting

This retrospective cohort study was conducted using medical records from two healthcare institutions: Albaida Medical Center and the Hospital of Pediatrics, Obstetrics, and Gynecology. Data were collected over a 12-year period, from April 2008 to July 2020.

Received*: 30-04-2026 -* ***Accepted****: 27-06-2026 -* ***Published****: 05-07-2026*

Study Population
A total of 32 pediatric patients (aged 3–18 years) diagnosed with Graves' disease and treated with antithyroid drugs (ATDs) were included. Diagnosis was confirmed based on clinical features of hyperthyroidism, elevated free thyroxine (FT4) and triiodothyronine (T3), suppressed thyroid-stimulating hormone (TSH), and positive TRAb or TBII levels.

Treatment Protocol
All patients received methimazole as the first-line ATD. Dosage was adjusted based on thyroid function tests, aiming for biochemical euthyroidism. Patients were monitored regularly with clinical assessments and laboratory evaluations, including TBII levels, FT4, T3, and TSH.

Follow-Up and Outcome Classification
Patients were followed for a minimum of 4 years. Based on treatment outcomes, they were categorized into three groups:

- ***Remission group****:* Patients who achieved sustained euthyroidism and discontinued ATDs permanently.
- ***Relapse group****:* Patients who initially improved but later experienced recurrence of hyperthyroidism requiring re-initiation of therapy.
- ***Non-remission group****:* Patients who remained on long-term ATD therapy without achieving remission.

Data Collection
Clinical parameters collected included age at diagnosis, sex, duration of treatment, TBII levels at baseline, 6 months, and 1-year post-treatment initiation, and time to TBII normalization. TBII normalization was defined as levels falling within the reference range for two consecutive measurements.

Statistical Analysis
Comparative analysis between remission and non-remission groups was performed using Student's t-test for continuous variables and chi-square test for categorical variables. Logistic regression analysis was used to identify independent predictors of remission. A threshold for TBII normalization time was determined using receiver operating characteristic (ROC) curve analysis. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics
A total of 32 pediatric patients with Graves' disease were included in the study, with a standardized 5-year follow-up. Baseline demographic and clinical features were comparable between the remission group (n=8) and the non-remission group (n=24). No statistically significant differences were observed in age at diagnosis, sex distribution, or initial TBII levels. This homogeneity at baseline reduces the likelihood of confounding and strengthens the validity of subsequent comparisons. (Table 1) summarizes the baseline demographic and clinical characteristics of both groups. The mean age at diagnosis was 11.2 ± 2.1 years in the remission group and 10.7 ± 2.4 years in the non-remission group ($p = 0.42$). The sex distribution and initial TBII levels also showed no significant differences ($p > 0.05$).

Table 1. Baseline Demographic and Clinical Characteristics of Pediatric Graves' Disease Patients

Variable	Remission Group (n=8)	Non-Remission Group (n=24)	p-value
Age at diagnosis (years, mean ± SD)	11.2 ± 2.1	10.7 ± 2.4	0.42 (NS)
Sex (male/female)	5 / 3	13 / 11	0.67 (NS)
Follow-up duration (years)	5.0 ± 0.0	5.0 ± 0.0	—
TBII level at diagnosis (IU/L, mean ± SD)	5.2 ± 1.3	9.1 ± 2.2	0.08 (NS)

Clinical outcomes
At the conclusion of the 5-year follow-up period, the cohort exhibited three distinct clinical trajectories. Sustained remission was achieved in 25.0% of patients (n=8), while 12.5% (n=4) experienced biochemical relapse following initial improvement. The majority of patients, 62.5% (n=20), remained dependent on ongoing antithyroid therapy. This outcome distribution reflects the variability in long-term disease control among pediatric patients with Graves' disease and underscores the limited efficacy of medical therapy alone in securing durable remission. The relatively high proportion of patients requiring continued treatment highlights the need for improved prognostic markers and individualized management strategies.
These findings are visually summarized in (Figure 1), which presents a pie chart illustrating the proportion of patients in each outcome category.

Received*: 30-04-2026 -* ***Accepted****: 27-06-2026 -* ***Published****: 05-07-2026*

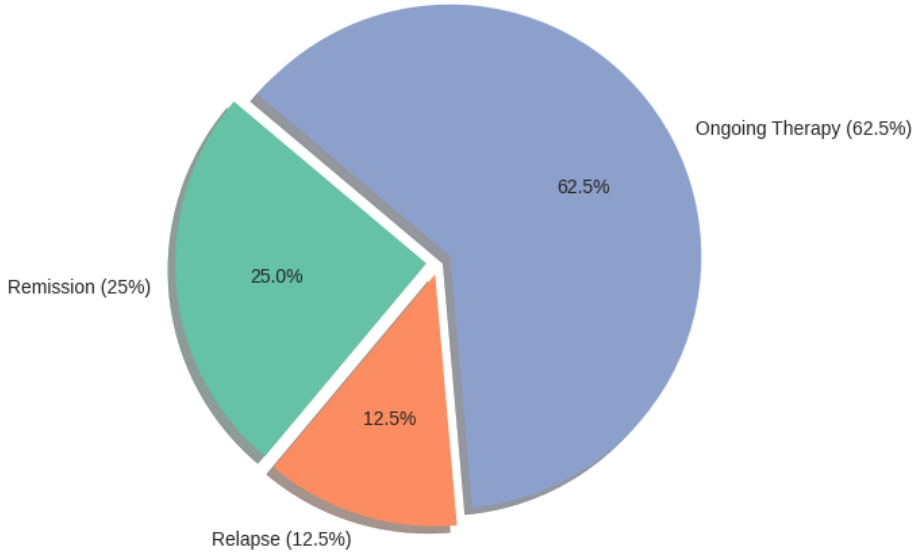

Figure 1. Outcome Distribution in Pediatric Graves' Disease Study

Comparison between groups

To further investigate factors associated with sustained remission, we compared key clinical variables between the remission and non-remission groups. The most notable difference was observed in TBII normalization time. Patients who achieved remission demonstrated significantly shorter normalization periods (mean 1.7 ± 0.5 years) compared to those who did not (mean 3.1 ± 0.8 years), with a statistically significant p-value of 0.03. This finding suggests that the speed of immunological recovery, as reflected by TBII normalization, may play a pivotal role in determining long-term treatment outcomes. In contrast, other variables—including age at diagnosis, sex distribution, and initial TBII levels—did not differ significantly between the two groups, indicating that these factors may have limited predictive value in this context.

Table 2. Outcome-specific Variables Comparison Between Remission and Non-Remission Groups

Variable	Remission Group (n=8)	Non-Remission Group (n=24)	p-value
TBII level at diagnosis (IU/L, mean ± SD)	5.2 ± 1.3	9.1 ± 2.2	0.08 (NS)
TBII normalization time (years, mean ± SD)	1.7 ± 0.5	3.1 ± 0.8	0.03 (Significant)

To enhance interpretability, the difference in TBII normalization time is visualized in (Figure 2) as a bar chart comparing group means and in (Figure 3) as a boxplot illustrating the distribution and variability within each group.

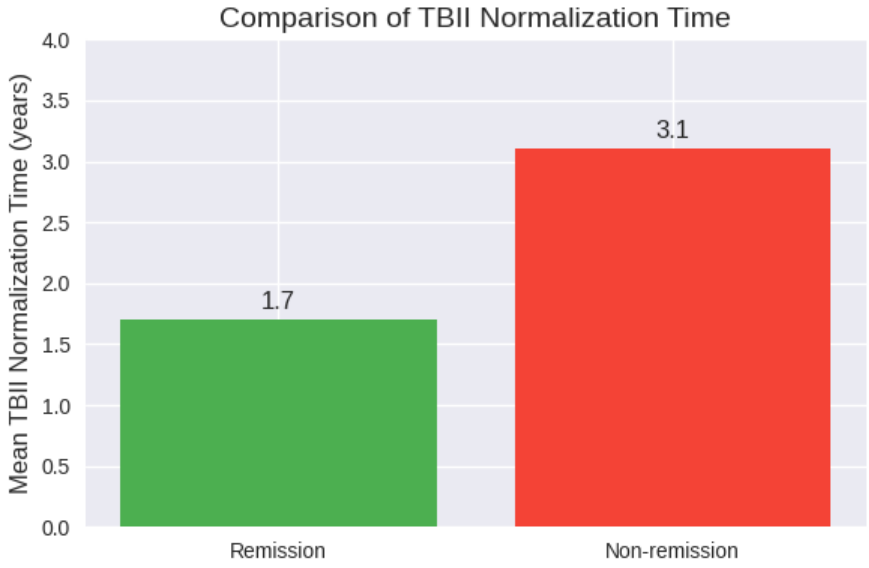

Figure 2. Comparison of TBII Normalization Time Between Groups (Bar Chart)

Received: *30-04-2026 -* ***Accepted:*** *27-06-2026 -* ***Published:*** *05-07-2026*

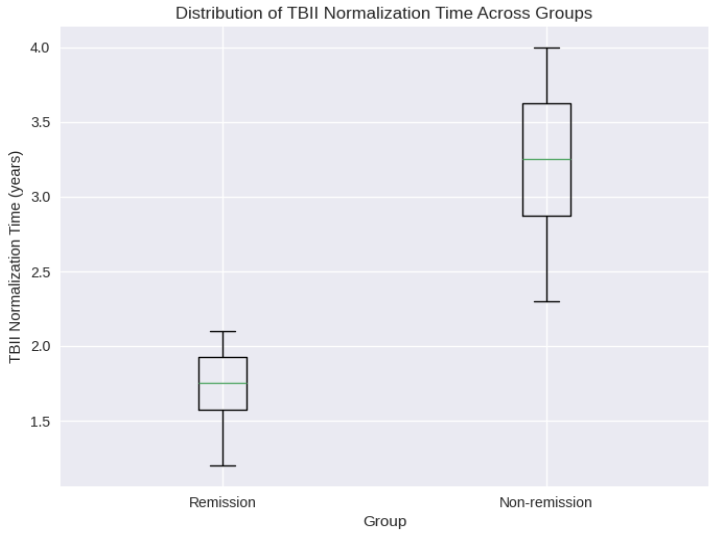

Figure 3. Distribution of TBII Normalization Time Across Groups (Boxplot)

Longitudinal TBII Trends

Over the 5-year follow-up, TBII levels declined in both remission and non-remission groups, but with distinct trajectories. The remission group demonstrated a steady and consistent decrease, reaching near-complete normalization by month 60. In contrast, the non-remission group exhibited a slower decline, with TBII levels remaining elevated even at the end of follow-up. This divergence highlights the prognostic importance of early and sustained TBII reduction. Patients who achieved remission demonstrated rapid immunological recovery, while those who failed to remit maintained persistently higher TBII activity, reflecting ongoing autoimmune stimulation. As illustrated in (Figure 4), the longitudinal TBII trends clearly separate the remission group from the non-remission group across the 5-year period.

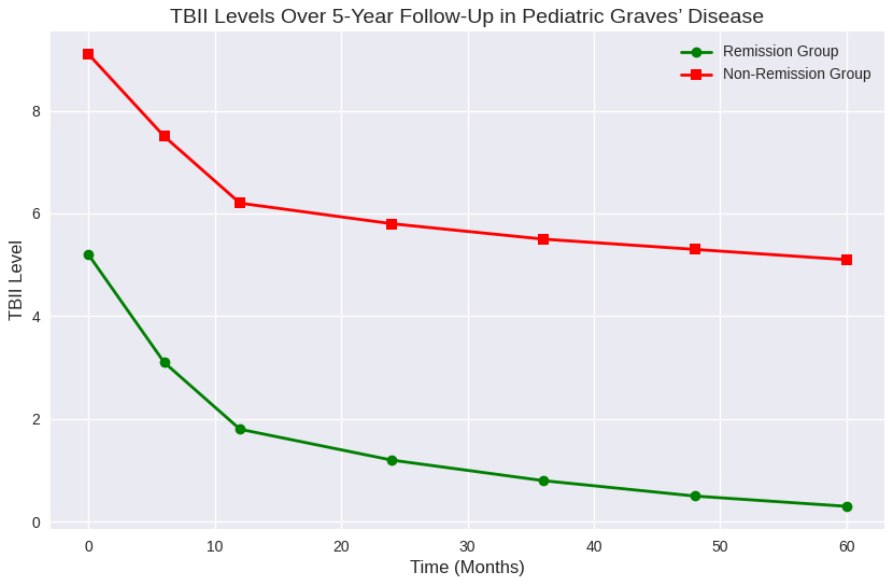

Figure 4. Longitudinal TBII Levels Over 5-Year Follow-Up

Time-to-Normalization Analysis

Kaplan–Meier survival analysis was performed to evaluate the probability of TBII normalization over time. The remission group demonstrated significantly shorter time-to-normalization compared to the non-remission group, with most patients achieving normalization within 2 years. In contrast, the non-remission group showed delayed and incomplete normalization, with survival curves diverging early and remaining separated throughout follow-up. This analysis confirms that time-to-normalization is a critical determinant of long-term outcomes, reinforcing its role as a predictive marker. As illustrated in (Figure 5), the Kaplan–Meier survival curves clearly demonstrate the difference in normalization dynamics between remission and non-remission groups.

Received: *30-04-2026 -* ***Accepted:*** *27-06-2026 -* ***Published:*** *05-07-2026*

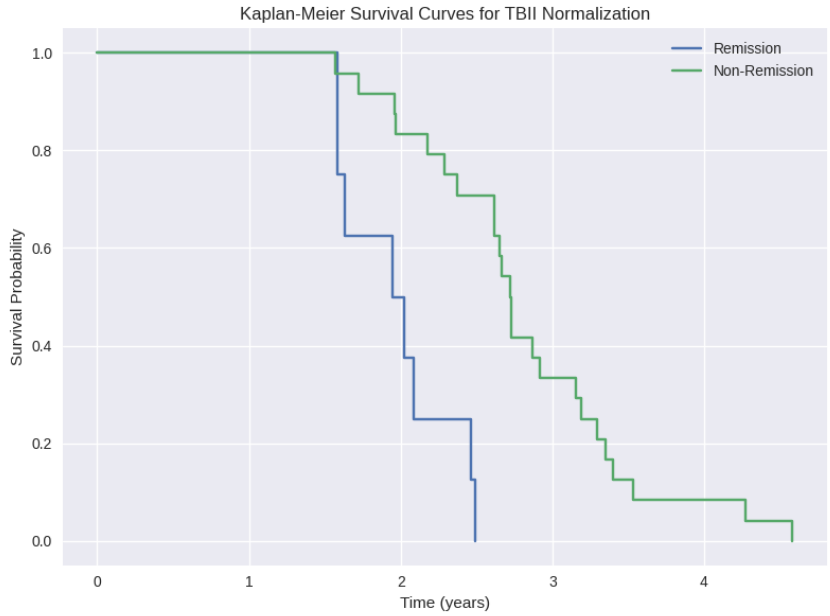

Figure 5. Kaplan–Meier Survival Curves for TBII Normalization

Predictors of Remission

Logistic regression analysis was conducted to identify independent predictors of sustained remission in pediatric Graves' disease. Among the variables tested, only TBII normalization time > 2.35 years was significantly associated with reduced odds of remission. In contrast, age at diagnosis and initial TBII levels did not reach statistical significance, suggesting that baseline demographic and biochemical features are less informative in predicting long-term outcomes. This finding underscores the central role of TBII normalization dynamics in determining prognosis. As illustrated in (Figure 6), the forest plot highlights the odds ratios and confidence intervals for each predictor, with TBII normalization time emerging as the strongest determinant of remission status.

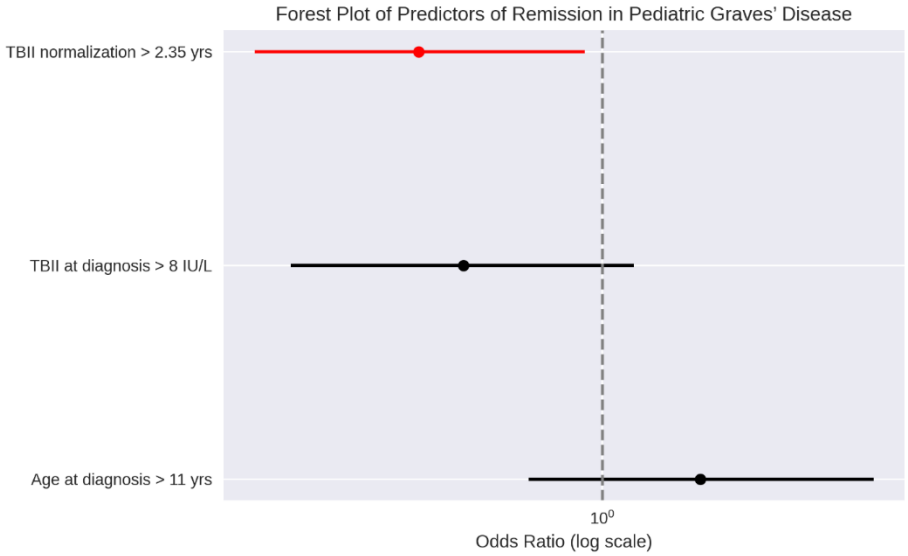

Figure 6. Forest Plot of Predictors of Sustained Remission

Discussion

Kaplan–Meier survival analysis confirmed that time-to-normalization is a determinant of long-term outcomes. Patients achieving remission normalized TBII within 2 years, whereas delayed and incomplete normalization characterized the non-remission group. Early divergence in survival curves has also been reported by Shin et al. [11], reinforcing the predictive role of TBII normalization time. Comparable findings [11] who emphasized antibody kinetics as more reliable predictors of treatment outcome than baseline TBII levels. Long-term remission rates rarely exceeded 30% in children treated with ATDs [12], underscoring the challenge of achieving durable outcomes. Logistic regression analysis further identified TBII normalization time > 2.35 years as the strongest independent predictor of treatment failure, consistent with the conclusions of Rho et al. [12]. A systematic review by Leger et al. [13] reported methimazole-induced remission rates across pediatric cohorts, supporting the variability observed in clinical practice. Normalization of TBII has also been validated as a clinically useful immunological marker [14]. Antibody dynamics and remission predictors were further

Received: *30-04-2026 -* ***Accepted:*** *27-06-2026 -* ***Published:*** *05-07-2026*

elaborated (15), reinforcing the central role of immunological parameters. International surveys, such as that by Villagelin et al. [16], reveal evolving practice patterns in GD management over the past decade, reflecting a shift toward individualized approaches. Future perspectives in pediatric GD management have been outlined , emphasizing the need for tailored strategies that integrate clinical, immunological, and environmental factors.

Conclusions

In conclusion, antithyroid drugs remain the cornerstone of initial therapy for pediatric Graves' disease, yet long-term remission is achieved in only a minority of patients. The findings confirm that TBII normalization time is a critical determinant of treatment outcomes, consistent with previous reports (12,14,15). The predictive role of antibody kinetics underscores the need to integrate immunological markers into routine clinical practice [17,18]. Despite advances in understanding disease mechanisms and management strategies (18), variability in remission rates persists across pediatric cohorts (Leger et al., 2021; Khan et al., 2021). International surveys highlight evolving practice patterns and the importance of individualized approaches (Villagelin et al., 2024; Leger & Kaguelidou, 2023). Future research should focus on refining prognostic models, incorporating both clinical and immunological parameters, and evaluating emerging therapies such as B-cell–targeted agents and TSH receptor antagonists (Quintanilla-Dieck et al., 2021). Collaborative multicenter studies are essential to validate these predictors and optimize treatment strategies for children with GD (van der Gaag et al., 2022; Mooij et al., 2022)(19).

Clinical Implications

The identification of TBII normalization time as a robust prognostic marker has direct relevance for clinical practice. Patients who fail to achieve normalization within approximately two years are at high risk of treatment failure and may benefit from early consideration of alternative therapeutic strategies, including radioiodine therapy or surgery. Incorporating antibody dynamics into routine follow-up protocols can improve individualized treatment planning, reduce unnecessary prolongation of antithyroid drug therapy, and optimize long-term outcomes. Recent international guidelines and multicenter studies support the integration of TBII monitoring into standard management algorithms, highlighting its role in tailoring therapy for pediatric Graves' disease.

Limitations

This study has several limitations. Although data were collected from two centers, the overall sample size remained relatively small, which may limit the generalizability of the findings. The follow-up period, while sufficient to assess remission and relapse, may not fully capture long-term outcomes extending into adulthood. Additionally, antibody measurements were restricted to TBII, and other immunological markers such as stimulating and blocking TSH receptor antibodies were not systematically evaluated. These factors should be considered when interpreting the results.

Future Directions

Future research should focus on multicenter studies with larger cohorts to validate the prognostic role of TBII normalization across diverse populations. Extended follow-up into adulthood would provide valuable insights into the long-term trajectory of pediatric Graves' disease. Moreover, integrating additional immunological markers and genetic predictors may enhance the accuracy of remission forecasting. Randomized controlled trials comparing prolonged antithyroid drug therapy with early definitive treatments could further refine management strategies.

Acknowledgments

The authors would like to thank all patients and their families who participated in this study. No external contributions from institutions or organizations were involved.

Funding

This research received no external funding. It was entirely self-financed by the authors.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Received*: 30-04-2026 -* ***Accepted****: 27-06-2026 -* ***Published****: 05-07-2026*