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Real-World Data on the Development of Relapse in Graves' Disease from a Tertiary Referral Center

Graves Hastalığı'nda Nüks Gelişimi: Üçüncü Basamak Referans Merkezin Gerçek Yaşam Verileri

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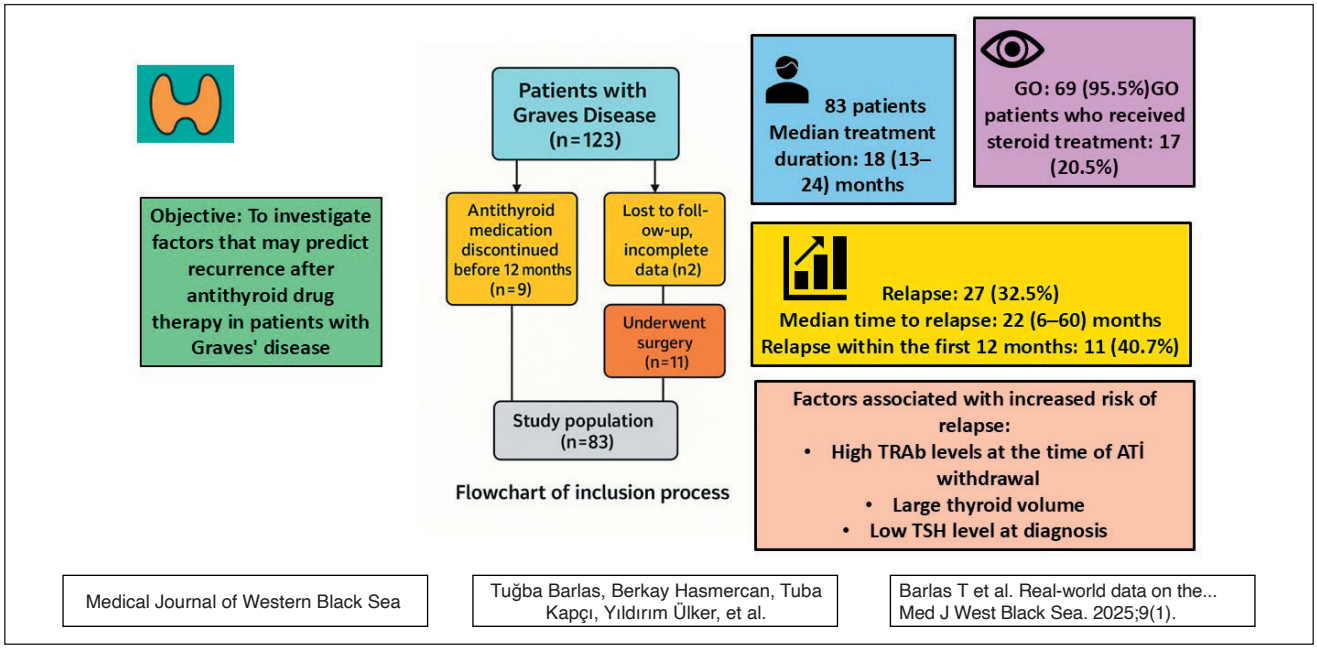
GRAPHICAL ABSTRACT



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ABSTRACT

Aim: We aimed to evaluate clinical and laboratory parameters that may predict relapse in patients who have received adequate antithyroid drug (ATD) therapy for Graves' disease (GD).

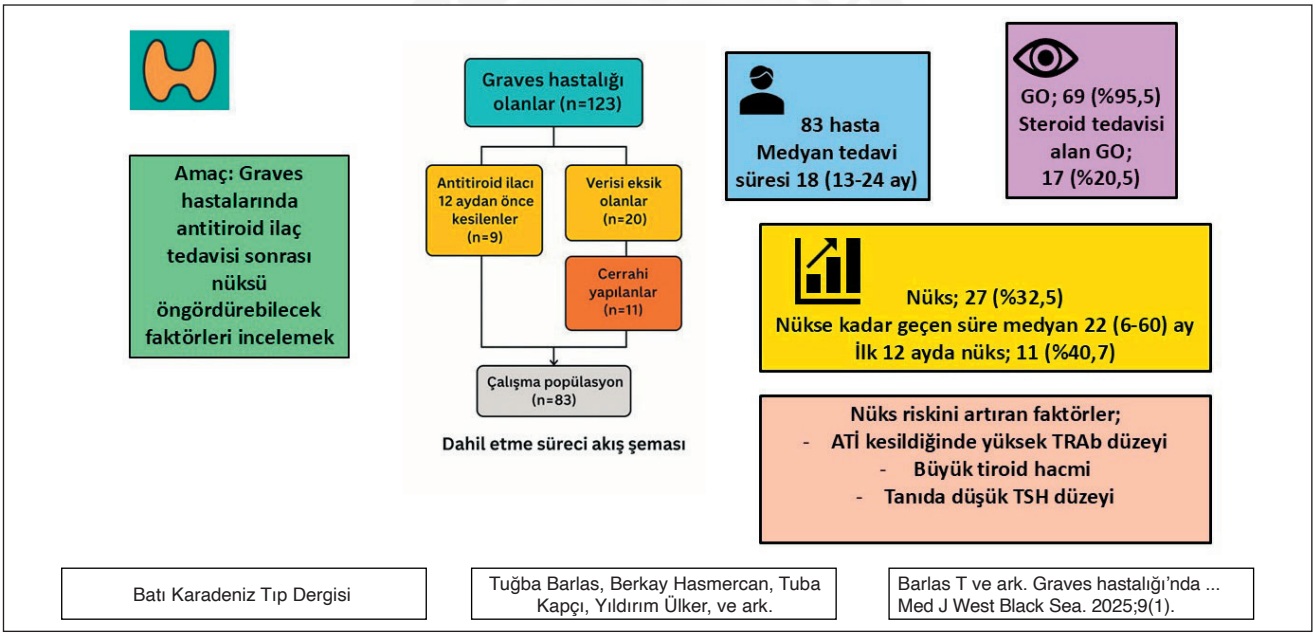
Material and Methods: We included patients with GD who received ATD therapy for at least 12 months and were followed for at least 12 months after treatment. Patients were classified into relapse and non-relapse groups, and their demographical, laboratory, imaging findings, and follow-up information were recorded retrospectively.

Results: Eighty-three patients were included, with a median treatment duration of 18 (13-24) month. Graves' orbitopathy (GO) was present in 58 (69.9%) of patients, and 17 (20.5%) received steroid therapy for GO. Relapse occurred in 27 (32.5%) of patients, with a median time to relapse of 22 (6-60) months, and 11 (40.7%) relapsed within the first 12 months. No association was found between TRAb positivity at diagnosis and relapse (p=0.542), but higher TRAb levels at ATD discontinuation (p=0.026), larger thyroid volumes (p=0.043), and lower TSH levels at diagnosis (p=0.027) were related with increased relapse risk. In the whole patient group, GH relapse was lower in those treated with corticosteroids as GO therapy (p=0.030). The regression model identified thyroid volume (p=0.044) and corticosteroid usage for GO (p=0.042) as predictors of relapse.

Conclusion: Our findings suggest that while GH relapse might be more frequent in patients with larger thyroid volumes, corticosteroid therapy administered for GO may serve as a protective factor for GH relaps. The real-world data from our tertiary referral center may contribute to studies on GD relapse development, especially when considering sociodemographical differences.

Keywords: Antithyroid drugs, corticosteroid therapy, Graves' orbitopathy, hyperthyroidism, thyrotoxicosis

GRAFİKSEL ÖZET



ÖZ

Amaç: Graves Hastalığı (GH) için yeterli antitiroid ilaç (ATİ) tedavisi almış hastalarda nüksü öngördürebilecek klinik ve laboratuvar parametrelerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: En az 12 ay boyunca ATİ tedavisi almış ve tedavi sonrası en az 12 ay takip edilmiş GH olan hastalar çalışmaya dahil edildi. Hastalar, nüks ve nüks olmayan gruplar olarak sınıflandırıldı. Hastaların demografik, laboratuvar, görüntüleme bulguları ile takip verileri retrospektif olarak kaydedildi.

Bulgular: Toplam 83 hasta çalışmaya dahil edildi ve medyan tedavi süresi 18 (13-24) aydı. Hastaların 58 (%69,9)'inde Graves orbitopatisi (GO) mevcuttu ve 17 (%20,5)'si GO için steroid tedavisi almıştı. Hastaların 27 (%32,5)'sinde nüks gelişmişti ve nükse kadar geçen süre medyan 22 (6-60) aydı. Nüks gelişen hastaların 11 (%40,7)'sinde nüks ilk 12 ay içinde gelişmişti. Tanı sırasındaki TRAb pozitifliği ile nüks gelişimi arasında bir ilişki bulunmadı (p=0,542), ancak ATİ tedavisinin kesilmesi sırasında daha yüksek TRAb seviyeleri (p=0,026), daha büyük tiroid hacmi (p=0,043), ve tanı anında daha düşük TSH seviyeleri (p=0,027) artmış nüks riski ile ilişkili bulundu. Tüm hasta grubunda GO tedavisi olarak steroid uygulananlarda GH nüks sıklığı daha düşüktü (p=0,030). Regresyon modelinde, tiroid hacmi (p=0,044) ve GO için kortikosteroid kullanımı (p=0,042) nüks gelişimi ile ilişkili faktörler olarak saptandı.

Sonuç: Tiroid hacmi daha yüksek olanlarda GH nüksü daha fazla gözlenebilirken, GO'da uygulanan kortikosteroid tedavisi nüks gelişimi üzerinde koruyucu bir faktör olabilir. Bulgularımız, özellikle sosyodemografik farklılıklar göz önünde bulundurulduğunda, GH'de nüks gelişimi üzerine yapılan çalışmalara ek katkı sağlayabilir.

Anahtar Sözcükler: Antitiroid ilaç, Graves orbitopatisi, hipertiroidi, kortikosteroid tedavi, tirotoksikoz

INTRODUCTION

Graves' disease (GD) is an autoimmune disorder in which the thyroid gland is targeted by the immune system (1). In areas with sufficient iodine, GD is the most common cause of hyperthyroidism, with an incidence of 20–30 cases per 100,000 people each year (2). GD can lead to an increase in long-term morbidity and mortality, as well as an impairment in quality of life. The objectives of treatment are to safely and promptly restore thyroid function, prevent recurrence and adverse effects of therapy, and maintain long-term normal thyroid function, as GD has a significant impact on affected individuals (3).

The treatment options for GD include antithyroid drugs (ATD), radioactive iodine (RAI), and surgery. The choice of initial and subsequent treatments often depends on local standards and practices (4). The European Thyroid Association Guidelines recommend ATD as the initial treatment for GD, especially in younger individuals (1). The optimal duration of ATD therapy using the titration regimen is 12–18 months, with maximum remission rates of 50–55% achieved within this period (5-7). It is recommended to measure the thyroid-stimulating hormone receptor antibody (TRAb) levels before discontinuing ATD therapy, as normal levels suggest a higher likelihood of remission (6, 8). Relapse is most common within the first 6–12 months after stopping ATD but can occur years later (1). However, predicting relapse and identifying risk factors might be challenging due to the autoimmune nature of the disease. The existing literature indicates that certain factors, such as severe hyperthyroidism, large goiters, and persistently high TRAb titers, can make remission more difficult and increase relapse risk (9-11). Furthermore, there are studies aiming to predict relapse risk using models that combine clinical and genetic markers (12-14). However, the efficacy of numerous clinical and laboratory parameters in predicting the risk of relapse in clinical practice remains controversial. In this study, we aim to evaluate clinical and laboratory parameters that may predict relapse in patients who have received adequate ATD therapy for GD.

MATERIALS and METHODS

Study Design and Participants

The study was conducted retrospectively from January 2016 to June 2024 at an outpatient clinic of the Endocrinology and Metabolism Department of a tertiary center. It was approved by the Ethical Committee of Gazi University. The study included patients who were diagnosed with GD, underwent at least 12 months of ATD therapy, and were monitored for at least 12 months after ATD cessation. The patients were grouped into relapse and nonrelapse. The exclusion criteria were as follows: (i) patients with an uncertain diagnosis of GD; (ii) patients who discontinued their ATD treatment before 12 months; (iii) patients who were followed up for less than 12 months after discontinuing ATD; (iv) patients who underwent surgery or RAI as their initial treatment for hyperthyroidism; and (v) patients with a hyperthyroidism etiology other than GD; (vi) pregnancy, major illness, or medical treatment influencing thyroid function. The flowchart of inclusion process was provided in Figure 1.

Data Collection and Definitions

Patients' demographical features, past medical histories, laboratory and imaging findings, and follow-up data were obtained from medical records. The diagnosis of GD was established based on the following criteria: serum thyroid-stimulating hormone (TSH) levels below the lower normal limit, accompanied by elevated free thyroxine (fT4) and/or free triiodothyronine (fT3) levels, along with increased serum TRAb levels and/or increased radioactive iodine uptake. Additionally, appropriate clinical features such as symptoms of hyperthyroidism, a diffuse goiter (as defined by ultrasonography), or Graves orbitopathy (GO) were considered. Relapse was defined as the occurrence of hyperthyroidism, indicated by fT4 or fT3 levels above the upper normal limit and TSH levels below the lower normal limit, at any point during the follow-up period (1).

Laboratory parameters such as neutrophil, lymphocyte, alanine aminotransferase (ALT), aspartate aminotransferase (AST), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, and vitamin D levels at the time of the initial diagnosis were recorded. TRAb level was recorded as negative, 1-2 times higher or higher than 2 times of upper limit normal (ULN). Thyroid volume was calculated using the formula 0.479 × length (cm) × width (cm) × height (cm) (15).

Statistical Analysis

Statistical analyses were conducted using SPSS version 22.0. The Shapiro-Wilk test assessed the normality of con-

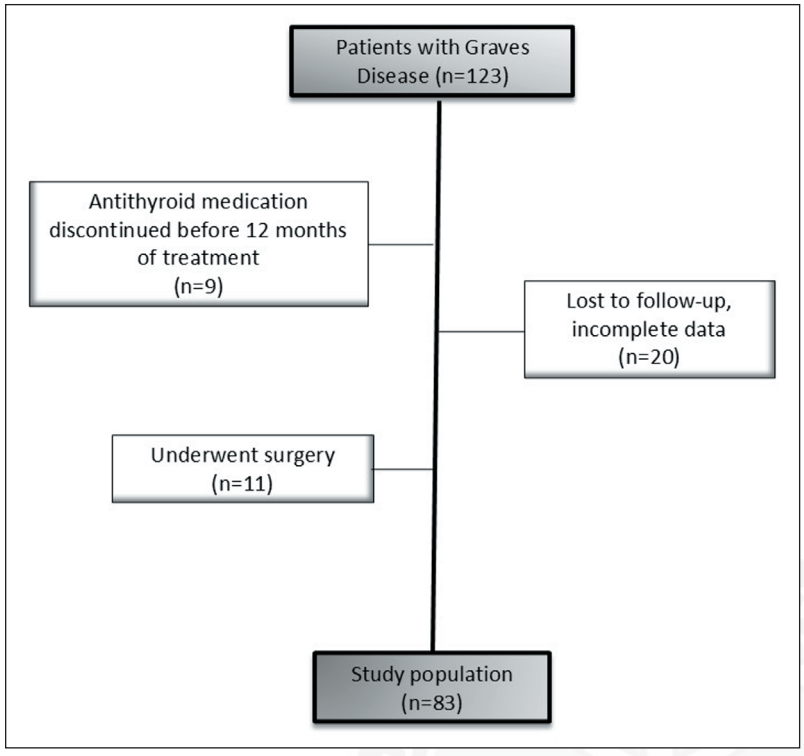


Figure 1: Flowchart of inclusion process

tinuous data. We reported normally distributed continuous variables as mean and standard deviation, and presented non-normally distributed variables as median and interquartile range. The Mann-Whitney U, independent sample t test compared continuous variables. The $\chi 2$ (chi-squared) and Fisher's exact tests compared categorical variables. A multivariate logistic regression analysis was conducted to determine the factors that affect the relapse of GD. The threshold for statistical significance was established at $p < 0.05$.

RESULTS

After applying exclusion criteria, a total of 83 patients were included in the study. The mean age of the patients was 46.5±12.5 years, and 62 (74.7%) patients were female. The median treatment duration was 18 (13-24) months. A total of 38 patients (45.8%) were smokers. GO was present in 58 patients (69.9%), and 17 patients (20.5%) had received steroid therapy for GO.

In our study, relapse occurred in a total of 27 patients (32.5%). Among these cases, relapse occurred within the first 12 months in 11 patients (40.7%). The median time to relapse was 22 (6-60) months. The median follow-up duration for the group without relapse was 39 (30-56) months. The characteristics of patients with and without relapse are summarized in Table 1. No association was found between TRAb positivity at the time of diagnosis and relapse. However, an increased relapse rate was observed in patients with higher TRAb levels at the time of ATD discontinuation. Furthermore, patients with larger thyroid volumes and lower TSH levels at diagnosis exhibited a higher incidence of relapse. In the whole patient group, GH relapse was lower in those treated with corticosteroids as GO therapy. In the regression model developed to predict relapse risk, it was found that thyroid volume and the administration of steroids for GO treatment were associated with relapse (Table 2).

DISCUSSION

In our study, the relapse rate of GD was found to be 32.5%. While varying results have been reported in the literature, a meta-analysis including 3,242 patients found relapse rates as high as 51.9% (11). Since the risk of relapse is significantly increased and it also affects the choice of treatment, certain factors in predicting the risk of relapse were investigated. Moreover, some scoring systems have been developed to assess relapse risk of GD (13). Factors such as younger age, large goiter, smoking, male sex, higher TRAb levels, longer therapy duration, and elevated thyroid hormone levels have been considered to have an impact for relapse (11, 13, 16, 17). However, the combined influence of various genetic, developmental, immunological, and environmental factors can lead to different outcomes (18). In our study, higher thyroid volume was found to be related with the development of relapse. Supporting our findings, Liu et al. (9) demonstrated that, in addition to larger goiter size, higher TRAb levels, and lower TSH levels at the time

Table 1. Characteristics of the patients with Graves disease

	Patients with relapse, n=27	Patients without relapse, n=56	p value
Age, years	48.4 ± 12.7	45.6 ± 12.4	0.344
Gender, Female, n (%)	21 (77.8)	41 (73.2)	0.654
Smoking, n (%)	9 (33.3)	29 (51.8)	0.143
GO, n (%)	16 (59.3)	42 (75.0)	0.143
Steroid therapy for GO, n (%)	2 (7.4)	15 (26.8)	**0.030**
ATD duration, months	18 (12-26)	18 (14-22)	0.883
TRAb positivity at diagnosis, n (%)	24 (88.9)	52 (92.9)	0.542
TPO positivity at diagnosis, n (%)	19 (70.4)	34 (60.7)	0.699
TRAb, at the end of the ATD therapy, n (%)			**0.026**
Negative	14 (51.9)	36 (54.3)	
Positive (1-2x)	7 (25.9)	3 (5.4)	
Positive (>2x)	6 (22.2)	17 (30.4)	
TSH at diagnosis, mIU/mL	0.01 (0.01-0.03)	0.01 (0.01-0.89)	**0.027**
sT3 at diagnosis, pg/mL	4.89 (3.86-11.90)	4.40 (3.51-11.18)	0.232
sT4 at diagnosis, ng/dL	2.31 (1.23-3.82)	1.40 (0.97-2.93)	0.072
NLR at diagnosis	1.8 (1.2-2.7)	1.7 (1.2-2.1)	0.292
ALT at diagnosis, U/L	21.9 ± 10.0	22.8 ± 11.9	0.928
AST at diagnosis, U/L	20.8 ± 6.5	21.0 ± 5.1	0.767
LDL at diagnosis, mg/dL	113.7 ± 32.8	111.4 ± 42.3	0.639
Thyroid volume, ml	22.3 (16.2-36.6)	14.7 (11.4-27.8)	**0.043**
ATD, n (%)			0.542
MMI	24 (88.9)	52 (92.9)	
PTU	3 (11.1)	4 (7.1)	

GO: Graves orbitopathy, **ATD:** Anti-thyroid drug, **TRAb:** Thyrotropin receptor antibodies, **TPO:** Thyroid peroxidase antibodies, **TSH:** Thyroid-stimulating hormone, **sT3:** Free triiodothyronine, **sT4:** Free thyroxine, **NLR:** Neutrophil-to-lymphocyte ratio, **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **LDL:** Low-density lipoprotein, **MMI:** Methimazole, **PTU:** Propylthiouracil

Table 2. The logistic regression model to predict relapse development

	Exp (B)	95% CI	p value
TSH at diagnosis, mIU/mL	2.40	0.54-10.64	0.250
Thyroid volume, ml	1.06	0.93-0.99	**0.044**
Steroid therapy for orbitopathy	0.10	0.11-0.92	**0.042**
TRAb, at the end of the ATD therapy	0.12	0.01-1.01	0.051
sT3 at diagnosis, pg/mL	1.03	0.93-1.15	0.524

TSH: Thyroid-stimulating hormone, **TRAb:** Thyrotropin receptor antibodies, **ATD:** Anti-thyroid drug, **sT3:** Free triiodothyronine
Nagelkerke R^2 value of the model was 0.332.

of GD diagnosis also play a role in the development of relapse. In the study by Tun et al. (19), the risk of relapse was found to be 58% in patients with TRAb levels <0.9 IU/L at the time of treatment cessation, whereas it was 82% in those with TRAb levels >1.5 IU/L. On the other hand, despite our study demonstrating a higher relapse rate in patients with lower initial TSH and higher TRAb level at the time of ATD discontinuation, the regression analysis did not reveal the influence of TSH and TRAb levels. This may be due to the fact that TSH levels at diagnosis were often too low to be measured in some patients as well as categorical analysis of TRAb levels.

Interestingly, in our study, patients who received corticosteroid therapy for the treatment of GO had a lower relapse frequency in whole patient group. Similarly, a study by Moli et al. (20) also reported a reduced relapse rate in patients treated with pulse steroid therapy for GO, with this effect being more pronounced in younger patients. The autoimmune nature of GD and the immunosuppressive effect of corticosteroid therapy could potentially explain this finding (1, 21). Furthermore, our study revealed a higher incidence of GO than previously reported in the literature, potentially due to our center's role as a tertiary referral center for GO management (22, 23).

Recent publications have emphasized that long-term low-dose ATD therapy may reduce the risk of relapse (16, 24,

25). We found no significant difference in ATD duration between patients who experienced relapse and those who did not. However, due to the retrospective design of our study, we did not include long-term low-dose treatment regimens, which can last up to approximately 14 years, as mentioned in a review by Azizi and Malboosbaf (24). This recommendation, which stands out among the modifiable risk factors for relapse, may potentially influence the general approach to the treatment of GD if further studies support it (26).

Additionally, while relapse in GD is generally reported to occur within the first 12 months, in our study, relapse was observed at a median of 22 months (22). This may be related to our center being a tertiary referral center for GO patients, the higher number of patients receiving immunosuppressive therapy for GO, as well as the fact that patients are closely monitored and followed up for longer periods without interruption.

Our study has certain limitations. Firstly, it is designed as a retrospective study and includes a limited number of patients. The results are difficult to generalize to the broader population because they were administered in a single center. However, it provides valuable insights into real-world data from a tertiary center. Additionally, due to changes in the reference range of TRAb levels over the years, numerical analysis could not be performed.

Our findings suggest that thyroid volume and corticosteroid treatment for GO might be associated with the development of relapse in GD. Various genetic and environmental factors are known to influence relapse in GD. We believe that investigating the factors contributing to relapse development in our study, based on real-world data from different populations and even individual centers, could provide valuable insights into relapse outcomes.

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None

Author Contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by **Tuğba Barlas, Füsun Baloş Törüner** and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflict of interest in relation with the present study.

Financial Support

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Ethical Approval

The study was approved by Gazi University Ethical Committee.

Review Process

Extremely and externally peer reviewed and accepted.

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