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# Treatment Outcomes and Adherence to Pegvisomant in Acromegaly: A Retrospective Study

**ABSTRACT**

**Objective:** To evaluate real-world outcomes and adherence to pegvisomant therapy in patients with acromegaly.

**Methods:** This retrospective study included patients who received pegvisomant for ≥6 months at the pituitary center between 2016 and 2024 with available clinical data. Data were extracted from medical charts and electronic health records. Variables recorded included demographic and clinical characteristics, maximum daily pegvisomant dose, remission status, radiologically confirmed tumor progression in patients with residual adenomas, history of adverse events (significant transaminase elevations or injection site reactions), and documented therapy interruption or discontinuation. Statistical analyses were performed using Statistical Package for the Social Sciences, version 20.0.

**Results:** The cohort comprised 24 females (52.2%) and 22 males (47.8%). Mean age at diagnosis was 38.22 ± 9.51 years, and mean disease duration was 148.02 ± 70.54 months. The mean maximum daily dose of pegvisomant was 17.93 ± 7.04 mg. Remission was achieved in 37 patients (80.4%). No significant elevations in transaminases were observed. Therapy was discontinued in 1 patient (2.2%) due to injection site erythema and pain. Among patients with residual adenomas (n = 38), tumor progression occurred in 1 patient (2.6%). Twenty-four patients (52.2%) experienced therapy interruption during follow-up. Female sex was associated with a higher likelihood of therapy interruption (Exp(B) = 1.166, $P$ = .040), and longer disease duration showed a trend toward increased risk (Exp(B) = 1.022, $P$ = .068).

**Conclusion:** Strategies to improve patient adherence should be considered when prescribing pegvisomant, an effective treatment for acromegaly.

**Keywords:** Acromegaly, pegvisomant, treatment adherence

## Introduction

Acromegaly is a chronic and insidiously progressive disorder characterized by somatic overgrowth, skeletal deformities, and multisystem involvement.[1,2] In the vast majority of cases, the condition is caused by a growth hormone (GH)-secreting pituitary adenoma.[3] If left untreated, acromegaly is associated with substantial morbidity and increased mortality.[4,5] Transsphenoidal surgery (TSS) represents the first-line treatment; however, surgical remission is not achieved in all patients.[6] In such instances, medical therapy becomes essential, with somatostatin receptor ligands (SRLs) constituting the cornerstone of postoperative management. Nevertheless, a considerable proportion of patients exhibit partial or inadequate biochemical responses to SRL therapy.[7,8]

For these patients, alternative therapeutic strategies are required. Among available options, pegvisomant has emerged as a highly effective treatment.[6,9] Pegvisomant is a GH receptor antagonist administered via subcutaneous injection, and its therapeutic efficacy is monitored by serum insulin-like growth factor 1 (IGF-1) concentrations.[9-12] Although pegvisomant is highly effective in achieving biochemical control, its long-term use may be limited by potential adverse effects and the need for daily subcutaneous administration.[13] While the efficacy and safety of pegvisomant have been well established in clinical trials, real-world evidence remains comparatively limited, particularly within specific patient populations.

A comprehensive understanding of patient characteristics, treatment responses, and adverse event profiles in routine clinical practice is crucial for guiding optimal therapeutic strategies. Accordingly, the primary objective of the present study was to evaluate the effectiveness of pegvisomant therapy in achieving biochemical disease control in patients with acromegaly treated at a tertiary referral center. Secondary objectives included assessing treatment safety,

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patient adherence, and factors contributing to therapy discontinuation. These findings are expected to provide insights that may inform clinical decision-making and optimize management strategies for patients with acromegaly in real-world settings.

## Material and Methods

### *Patients and Data Collection*

This study included patients who received pegvisomant therapy for at least 6 months between 2016 and 2024 at the Department of Endocrinology and Metabolism, İstanbul University-Cerrahpaşa, Faculty of Medicine, and had complete clinical data available. Relevant data were retrospectively extracted from medical charts and electronic health records. The collected variables comprised sex, age at diagnosis, disease duration, baseline GH levels, IGF-1 expressed as a ratio to the upper limit of normal (IGF-1/ULN), maximum tumor diameter on baseline imaging, prior medical therapies, and history of radiotherapy (RT), if applicable. Treatment-related data included the maximum daily pegvisomant dose, evidence of tumor progression during pegvisomant therapy in patients with residual adenoma, and documented adverse events, such as a significant elevation in transaminases or injection-site reactions. In addition, remission status during pegvisomant therapy, as well as any treatment interruption or permanent discontinuation during follow-up, was recorded.

### *Study Outcomes*

The study assessed biochemical disease control as the primary outcome, while secondary outcomes encompassed treatment safety, patient adherence, and factors influencing therapy interruption or discontinuation. Detailed definitions and assessments of these outcomes are provided in the following sections.

### *Definition of Remission*

Biochemical remission was defined as normalization of serum IGF-1 concentrations, adjusted for age and sex, following the addition of pegvisomant to the therapeutic regimen.[6]

### *Definition of Adverse Events*

Treatment-related adverse events were categorized as tumor progression, significant elevations in liver transaminases, and injection site reactions. These were subsequently defined as follows:

Tumor progression during pegvisomant therapy was defined as a radiologically confirmed increase of ≥20% in the volume of a residual pituitary adenoma on follow-up magnetic resonance imaging (MRI).[6,14-16] A significant elevation in transaminases was defined as an increase in serum alanine aminotransferase and/or aspartate aminotransferase levels exceeding 3 times the ULN, in the absence of alternative causes of hepatic injury.[6,16] Injection site reactions were defined as localized erythema, swelling, pain, or discomfort occurring at the site of pegvisomant administration.[6,16,17]

### *Definition of Therapy Interruption or Discontinuation*

Therapy interruption was defined as a temporary cessation of pegvisomant treatment for at least 30 consecutive days. This threshold was selected based on the clinical washout period for pegvisomant; previous studies have indicated that serum IGF-1 levels return to baseline approximately 4 weeks after discontinuation of the drug.[12] Thus, a 30-day gap represents a clinically significant loss of biochemical control rather than a minor dosage omission. Therapy discontinuation was defined as the permanent cessation of pegvisomant treatment during follow-up, either due to adverse events or at the patient's request.

### *Statistical Analysis*

All statistical analyses were performed using Statistical Package for the Social Sciences software, version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution are presented as mean ± standard deviation (SD), while non-normally distributed variables are presented as median with interquartile range. Categorical variables are expressed as frequencies and percentages. Normality of distribution was assessed using the Shapiro–Wilk test.

Due to the very low number of patients who permanently discontinued therapy (n = 1), no separate group was created for these patients; this patient was included in the group of those who experienced any interruption for descriptive analyses. For the regression analysis evaluating factors associated with treatment interruptions, only patients with temporary interruptions were included to avoid bias, and the permanently discontinued patient was excluded.

Depending on the data type and distribution, the independent samples *t*-test or Mann–Whitney *U*-test was used for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Binary logistic regression analysis was performed to identify potential predictors of treatment interruption. To avoid overfitting, the number of variables included in the multivariable model was limited due to the small number of events.

A *P* value <.05 was considered statistically significant. All analyses were conducted in accordance with the predefined primary and secondary outcomes.

The study was approved by the Ethics Committee for Non-Interventional Clinical Studies of İstanbul University - Cerrahpaşa (Decision No: 2025/28; Date: January 8, 2025). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki (2013) and its later amendments. Written informed consent was obtained from patients who agreed to participate in the study.

## Results

### *General Characteristics of the Study Population*

This retrospective cohort comprised 46 patients with acromegaly, including 24 females (52.2%) and 22 males (47.8%). The mean age

### MAIN POINTS

- Pegvisomant achieved high biochemical remission rates and demonstrated a favorable safety profile in a real-world cohort of patients with acromegaly.
- Treatment-related adverse events and radiological tumor progression were uncommon during pegvisomant therapy.
- More than half of the patients experienced temporary treatment interruptions during follow-up, which were associated with lower remission rates.
- Female sex was independently associated with a higher likelihood of treatment interruption.
- These findings highlight the importance of optimizing long-term treatment adherence to maximize the effectiveness of pegvisomant therapy.

at diagnosis was 38.22 ± 9.51 years. Forty-two patients (91.3%) had undergone at least 1 TSS prior to initiation of pegvisomant, and all patients had previously received SRL therapy. Pegvisomant was initiated at a daily dose of 10 mg in all cases. During follow-up, the maximum daily dose reached a mean of 17.93 ± 7.04 mg.

Biochemical remission under pegvisomant therapy was achieved in 37 patients (80.4%) during follow-up. No cases of significant transaminase elevation were observed. Treatment was discontinued in 1 patient (2.2%) due to a persistent injection site reaction (local erythema and pain). Among patients with residual adenomas (n = 38), tumor enlargement was detected in 1 patient (2.6%) on follow-up imaging; the growth was minimal, did not necessitate discontinuation of therapy, and remained stable during subsequent monitoring.

Although adverse events potentially related to pegvisomant were infrequent, 25 patients (54.3%) experienced at least 1 episode of treatment interruption or discontinuation. Analysis of these cases showed that only 1 was directly caused by a drug-related adverse effect (injection site reaction). The vast majority of interruptions were unrelated to the drug's pharmacological profile; instead, they stemmed from logistical barriers, administrative delays, and patient-related factors, including noncompliance or reluctance due to the burden of daily injections. Consequently, nearly all affected patients resumed therapy after a temporary hiatus, with permanent discontinuation occurring in only a single instance. Detailed demographic and clinical characteristics of the study population are provided in Table 1.

### *Clinical Characteristics According to Adherence to Pegvisomant Therapy*

Patients were stratified according to adherence to pegvisomant therapy, comparing those who experienced treatment interruption or discontinuation with those who maintained continuous therapy. A total of 25 patients had at least 1 episode of therapy interruption or permanent discontinuation; among them, 24 experienced temporary interruptions and subsequently resumed treatment, whereas only 1 patient permanently discontinued therapy. For the present analysis, this single patient was excluded, and all results are reported for the 24 patients who resumed therapy.

Patients with a history of interruption had a significantly longer disease duration than those who maintained uninterrupted treatment (170.72 ± 77.80 months vs. 124.52 ± 55.39 months; $P = .027$). A significant sex disparity was observed, with 69.6% of female patients experiencing interruption, compared with 36.4% of male patients ($P = .017$) (Figure 1). Biochemical remission rates also differed significantly between the groups; remission was achieved in 95.2% of patients who maintained continuous pegvisomant therapy, compared with 66.7% among those with a history of interruption ($P = .030$).

In contrast, no statistically significant differences were detected between the groups regarding age at diagnosis, baseline GH levels, or maximum tumor diameter ($P > .05$ for all comparisons). Furthermore, prior RT did not significantly affect treatment outcomes, with no differences observed between RT-treated and RT-naive patients in biochemical remission ($P = .707$) or treatment adherence ($P = .762$). Overall, continuous adherence to pegvisomant therapy was associated with higher remission rates, whereas longer disease duration and female sex were more frequent among patients who experienced temporary treatment interruptions. Detailed comparisons between the 2 groups are summarized in Table 2.

### *Predictors of Pegvisomant Interruption*

To identify potential predictors of treatment interruption, a binary logistic regression analysis was performed. The model incorporated variables with clinical significance and those showing a trend toward significance in univariate analyses, including sex, age at diagnosis, disease duration, and baseline GH and IGF-1/ULN levels. To ensure model stability and avoid overfitting given the sample size, the number of independent variables was carefully prioritized.

The analysis identified female sex as a significant independent predictor of treatment interruption, with females exhibiting a higher risk compared to males (Exp(B) = 1.166, $P = .040$). Although longer disease duration was positively associated with the likelihood of interruption, this trend did not reach statistical significance (Exp(B) = 1.022, $P = .068$) and should therefore be interpreted with caution. The

**Table 1. Demographic and Clinical Characteristics of the Study Population**

| | |
|---|---|
| Gender | |
| Female | 24 (52.2) |
| Male | 22 (47.8) |
| Age at diagnosis[a], years | 38.22 ± 9.51 |
| Disease duration, months | 148.02 ± 70.54 |
| GH level at diagnosis, ug/L | 31.95 ± 27.39 |
| IGF-1/ULN ratio at diagnosis | 3.47 ± 2.16 |
| Maximum tumor diameter at diagnosis, millimeter | 23.22 ± 11.02 |
| Number of TSS[b] | 1 [1-2] |
| Number of patients receiving SRL therapy | 46 (100) |
| Number of patients receiving cabergoline therapy | 37 (80.4) |
| Number of patients receiving RT | 15 (32.6) |
| Gamma knife | 10 |
| CyberKnife | 4 |
| Conventional RT | 1 |
| Maximum daily pegvisomant dose, mg | 17.93 ± 7.04 |
| Toxic hepatitis following pegvisomant therapy | 0 (0) |
| Adenoma enlargement following pegvisomant therapy[c] | 1 (2.6)[c] |
| Injection site complications following pegvisomant therapy | 1 (2.2) |
| Remission following pegvisomant therapy | 37 (80.4) |
| Interruptionor discontinuation of pegvisomant therapy at least once | 25 (54.3)[d] |

GH, growth hormone; IGF-1, insulin-like growth factor 1; IQR, interquartile range; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; RT, radiotherapy; SD, standard deviation; SRL, somatostatin receptor ligand; TSS, transsphenoidal surgery; ULN, upper limit of normal.

[a]Age at diagnosis was defined as the age at the first clinical evaluation showing elevated age-adjusted IGF-1, lack of GH suppression during OGTT, and a pituitary adenoma detected on MRI.

[b]Forty-two patients underwent TSS, whereas 4 patients declined surgical intervention.

[c]This variable was analyzed only in the subset of patients with residual adenomas (n = 38).

[d]Twenty-four patients experienced temporary interruptions, whereas 1 patient permanently discontinued therapy.

Data are presented as n (%), mean ± standard deviation (SD), or median [interquartile range (IQR)], as appropriate.

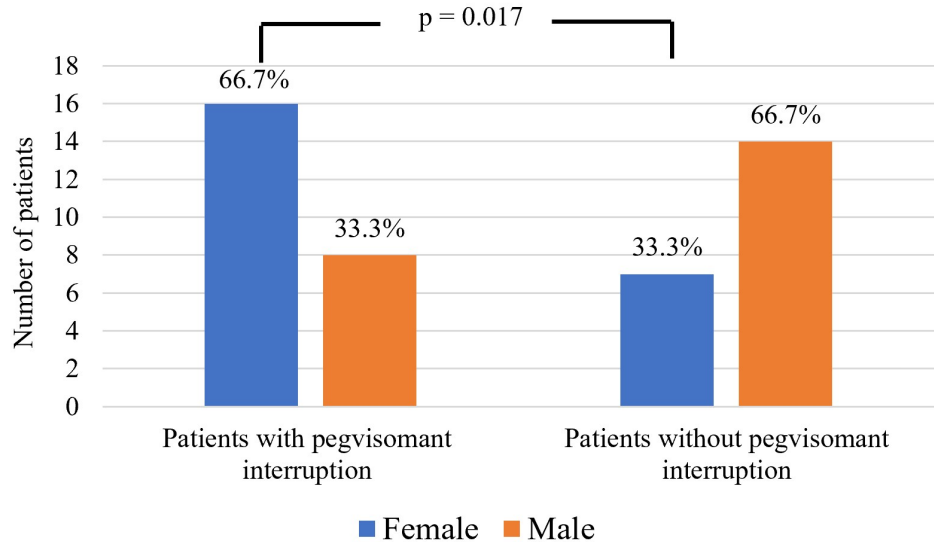


**Figure 1. Gender-based differences in pegvisomant therapy interruption.**

comprehensive results of the regression model are summarized in Table 3.

## Discussion

The present study provides real-world data on the effectiveness and safety of pegvisomant in patients with acromegaly managed at a tertiary referral center. High rates of biochemical remission were observed, and treatment was associated with a very low incidence of drug-related adverse effects, suggesting a favorable tolerability profile. These findings align with previously reported clinical and observational data supporting the efficacy and safety of pegvisomant in routine practice. Despite the favorable safety profile, more than half of the patients experienced temporary interruptions in therapy during follow-up. As expected, remission rates were notably lower among patients who did not maintain continuous treatment. Moreover, regression analysis identified female sex as an independent predictor of treatment interruption, while longer disease duration showed a trend toward increased likelihood of interruption.

**Table 2. Comparison Between Patients with and Without Pegvisomant Interruption**

| | Patients with Pegvisomant Interruption (n = 24) | Patients Without Pegvisomant Interruption (n = 21) | *P* |
|---|---|---|---|
| Characteristics | n (%) or mean ± SD | n (%) or mean ± SD | |
| Gender (F/M) | 16/8 | 7/14 | .017 |
| Age at diagnosis[a], years | 38.00 ± 9.02 | 38.90 ± 9.72 | .898 |
| Disease duration, months | 170.72 ± 77.80 | 124.52 ± 55.39 | .027 |
| GH level at diagnosis, ug/L | 30.95 ± 25.80 | 34.04 ± 29.18 | .666 |
| IGF-1/ULN ratio at diagnosis | 2.72 ± 1.30 | 4.01 ± 2.65 | .094 |
| Maximum tumor diameter at diagnosis, millimeter | 24.77 ± 9.93 | 21.54 ± 12.13 | .295 |
| Maximum daily pegvisomant dose, mg | 18.62 ± 7.68 | 18.10 ± 6.22 | .836 |
| Cabergoline use | 20 (83.3) | 17 (80.9) | .935 |
| Remission status | 16 (66.7) | 20 (95.2) | .030 |

F, female; GH, growth hormone; IGF-1, insulin-like growth factor 1; M, male; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; SD, standard deviation; ULN, upper limit of normal.
[a]Age at diagnosis was defined as the age at the first clinical evaluation showing elevated age-adjusted IGF-1, lack of GH suppression during OGTT, and a pituitary adenoma detected on MRI.

**Table 3. Logistic Regression Analysis Predicting Pegvisomant Interruption**

| Variable | B | SE | Wald | *P* | Exp(B) | 95% CI for Exp(B) |
|---|---|---|---|---|---|---|
| Gender (F) | 0.022 | 0.010 | 4.221 | .040 | 1.166 | 1.007-1.349 |
| Age at diagnosis | -0.016 | 0.055 | 0.090 | .765 | 0.984 | 0.883-1.095 |
| Disease duration | -1.947 | 1.066 | 3.336 | .068 | 1.022 | 1.001-1.043 |
| GH level at diagnosis | 0.001 | 0.016 | 0.007 | .934 | 1.001 | 0.971-1.033 |
| IGF-1/ULN ratio at diagnosis | -0.649 | 0.425 | 2.329 | .127 | 0.523 | 0.227-1.203 |

Exp(B), exponentiated regression coefficient; F, female; GH, growth hormone; IGF-1, insulin-like growth factor 1; SE, standard error; ULN, upper limit of normal.

Pegvisomant remains a cornerstone therapy for patients with acromegaly who fail to achieve biochemical control after surgery and SRL treatment. The addition of pegvisomant was associated with robust biochemical control in the study cohort, supporting its established role as an effective strategy in patients with persistent disease. These findings are consistent with long-term observational studies demonstrating sustained normalization of IGF-1 with continued pegvisomant therapy, both as monotherapy and in combination regimens.[18-20] Importantly, optimized dosing and close follow-up appear to be key contributors to long-term control, as suggested in previous prospective and registry-based data.[21-23]

The safety profile observed in the present study further reinforces the favorable tolerability of pegvisomant in routine practice. Despite longstanding concerns regarding hepatotoxicity and tumor growth, clinically relevant adverse events were uncommon.[22,24,25] Large real-world cohorts have similarly reported low rates of hepatobiliary complications and tumor progression, and variations in residual tumor size are increasingly considered more reflective of underlying disease biology than a direct pharmacological effect.[23,26] Collectively, these data reinforce the notion that pegvisomant can be used safely with appropriate biochemical and radiological monitoring.

Beyond efficacy and safety, the findings emphasize the critical importance of treatment continuity. Despite pegvisomant's favorable tolerability and low incidence of adverse events, a substantial proportion of patients experienced therapy interruptions, primarily due to non-pharmacological factors such as administrative delays, drug procurement issues, or the daily injection burden. Continuous therapy was strongly associated with higher remission rates, suggesting that sustained receptor blockade may be essential for optimal biochemical control. These observations highlight adherence as a key determinant of therapeutic success. However, caution is warranted, as reverse causality cannot be excluded. Patients with suboptimal biochemical response may have been more likely to interrupt treatment, highlighting a potentially bidirectional relationship between adherence and biochemical outcomes—a limitation inherent to the retrospective design. Moreover, although the retrospective nature of the study limits detailed sub-classification of all administrative reasons, the available data indicate that the drug's safety profile was not the primary driver of treatment interruptions in the cohort.

Importantly, the findings suggest practical strategies to improve adherence. These include structured patient education on the importance of continuous therapy, routine counseling to address injection fatigue and treatment burden, implementation of reminder systems for drug administration and follow-up visits, and a multidisciplinary approach involving endocrinologists, nurses, and pharmacists to proactively manage logistical barriers and psychosocial factors. While these strategies were not systematically applied in the retrospective cohort, incorporating them in clinical practice may help mitigate treatment interruptions and optimize long-term outcomes.

The trend toward an association between longer disease duration and treatment interruption may suggest that patients with longstanding disease, who have often been exposed to multiple therapeutic modalities over many years, could be more prone to treatment fatigue.[27] Chronic illness burden, injection fatigue, and psychological factors may contribute to reduced long-term persistence.[13] However, this observation should be interpreted cautiously, as the association did not reach conventional statistical significance. The observed association with female sex is more difficult to interpret, as previous studies have yielded inconsistent findings. While some cohorts report no gender-related differences in adherence,[28] others suggest higher rates of non-persistence among female patients.[29] Potential explanations may include psychosocial determinants, differing perceptions of treatment burden, or lifestyle-related factors; however, further pegvisomant-specific research is needed to clarify these associations. On the other hand, the regression analysis should be interpreted with caution given the limited number of events, which constrained the number of variables that could be included in the model. Although clinically relevant factors such as baseline IGF-1 levels, tumor characteristics, and prior therapies were considered, they could not be reliably incorporated due to the risk of model overfitting. Therefore, these findings should be interpreted as exploratory and hypothesis-generating rather than definitive.

Several limitations should be acknowledged. The retrospective, single-center design limits generalizability, and the available follow-up may not fully capture long-term outcomes. Additionally, irregular follow-up intervals and incomplete visit adherence prevented consistent calculation of a standardized follow-up duration, which was therefore not incorporated into the analysis. Consequently, differences in observation time may have influenced the likelihood of detecting treatment interruptions. Importantly, disease duration does not fully reflect time at risk and should not be interpreted as a surrogate for follow-up duration. All patients had received prior SRL therapy, and a substantial proportion also received cabergoline and/or RT, introducing treatment heterogeneity that limits the ability to isolate the independent effect of pegvisomant on biochemical remission. Moreover, IGF-1 levels at the time of pegvisomant initiation were not systematically available in the retrospective dataset and could not be included in the analysis. The relatively small sample size may also affect the statistical power of the predictive analysis. Although the number of events per variable was maintained at 12.5—exceeding the commonly recommended threshold of 10—the risk of model overfitting cannot be entirely excluded. Therefore, the identified predictors of treatment instability should be considered exploratory and should be validated in larger prospective cohorts. Nonetheless, this study provides real-world insight into treatment effectiveness, safety, and adherence patterns in a tertiary referral setting.

In conclusion, pegvisomant is an effective agent with a favorable safety profile for achieving biochemical control in acromegaly. However, long-term therapeutic success depends not only on pharmacological efficacy but also on sustained treatment adherence. Improving clinical outcomes requires a shift from merely prescribing the medication to actively supporting the patient's treatment journey. Targeted interventions, including structured patient education, routine counseling to address injection burden, reminder systems for medication administration and follow-up visits, and the simplification of logistical and administrative procedures, are essential to reduce treatment instability. Identifying patients at risk for treatment interruption, such as female patients or those with longer disease duration, and implementing these targeted strategies to support long-term persistence may be crucial for optimizing clinical outcomes.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Artificial Intelligence Usage Statement:** This study used ChatGPT (OpenAI) to improve the English language and grammar during the preparation of the manuscript.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee for Non-Interventional Clinical Studies of İstanbul University - Cerrahpaşa (Decision No: 2025/28; Date: January 8, 2025).

**Informed Consent:** Written informed consent was obtained from the patients/patient who agreed to take part in the study.

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