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Longitudinal Changes in FIB-4 Score During Androgen Deprivation Therapy in Patients with Prostate Cancer

ABSTRACT

Objective: Androgen deprivation therapy (ADT) is associated with adverse metabolic effects; however, its impact on noninvasive markers of liver fibrosis remains unclear. This study aimed to evaluate longitudinal changes in the FIB-4 score in patients with prostate cancer receiving luteinizing hormone–releasing hormone (LHRH) agonist therapy.

Methods: This retrospective study included 74 patients with prostate cancer treated with LHRH agonists. FIB-4 scores were assessed at baseline, 6 months, and 12 months. Longitudinal comparisons were performed among patients with complete data at all 3 time points (n = 42) using a Friedman test with Bonferroni pairwise comparisons.

Results: A total of 74 patients were included. Total prostate-specific antigen (PSA) and total testosterone levels decreased significantly after treatment ($P < .001$). Metabolic parameters, including HbA1c, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), remained unchanged after 6 months of ADT ($P > .05$). Among the 42 patients with complete follow-up, no significant change in FIB-4 score was observed at 6 months (adjusted $P = .243$); however, a significant increase was observed at 12 months (adjusted $P = .036$), with a median absolute change of 0.25 (Q1–Q3: −0.11 to 0.49; 95% CI: 0.07–0.62), indicating a time-dependent pattern.

Conclusion: FIB-4 scores remained stable during the early phase of LHRH agonist therapy but increased significantly at 12 months, indicating a delayed effect of ADT on liver fibrosis markers. These findings underscore the need for longitudinal monitoring of liver-related parameters in patients undergoing long-term ADT.

Keywords: Androgen deprivation therapy, liver fibrosis, metabolic dysfunction–associated steatotic liver disease, prostate cancer

Introduction

Prostate cancer is one of the most common malignancies in men and the second most frequently diagnosed cancer worldwide.[1] It remains a leading cause of cancer-related mortality among men.[2] For advanced and high-risk prostate cancer, androgen deprivation therapy (ADT) is the cornerstone of treatment because prostate gland growth and development depend on androgens.[3] The primary therapeutic goal of ADT is to achieve castration-level suppression of serum testosterone, typically with luteinizing hormone–releasing hormone (LHRH) agonists or antagonists.[4] In selected patients with high-risk localized or locally advanced disease, ADT is also a key component of multimodal therapy when combined with radiotherapy. In this context, initiating ADT before radiotherapy and continuing it afterward have been shown to improve survival outcomes.[5,6]

Androgen deprivation therapy has been associated with multiple metabolic adverse effects, including insulin resistance, dyslipidemia, and increased cardiovascular risk.[7] Emerging evidence also suggests a potential association between ADT and metabolic dysfunction–associated steatotic liver disease (MASLD), likely mediated through ADT-induced insulin resistance, visceral adiposity, and androgen deficiency.[8,9] Supporting this hypothesis, prior studies in hypogonadal men without prostate cancer have demonstrated an association between low serum testosterone levels and hepatic steatosis, even when testosterone concentrations are only mildly reduced.[10,11] In addition, population-based studies in men with prostate cancer have suggested an increased risk of steatotic liver disease and other hepatic outcomes among those receiving ADT, with evidence also indicating a possible dose–response relationship.[8]

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However, beyond hepatic steatosis, progression to liver fibrosis is a critical determinant of long-term hepatic and cardiovascular outcomes and remains insufficiently characterized in patients receiving ADT.[12] The FIB-4 score is a simple, widely used, noninvasive marker of liver fibrosis.[13] In this study, the authors aimed to evaluate temporal changes in FIB-4 scores among patients receiving ADT for prostate cancer.

Methods

Study Design and Population

This retrospective, single-center study was conducted at the Urology Department of Acıbadem Ankara Hospital from January 2017 to January 2025. A total of 74 patients with histologically confirmed prostate adenocarcinoma who received radiotherapy in combination with ADT were included.

Eligible patients had high-risk localized or locally advanced prostate cancer according to the European Association of Urology (EAU) risk classification.[14] High-risk disease was defined by the presence of International Society of Urological Pathology (ISUP) grade group 4-5 and/or clinical stage T3-4 and/or elevated prostate-specific antigen (PSA) levels. In addition, the study included patients deemed unsuitable for surgical treatment due to advanced age and/or frailty, as well as those who declined surgical treatment. All patients had no evidence of distant metastasis (M0). At diagnosis, all patients underwent prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT).

To prevent flare phenomenon, all patients were initiated on antiandrogen therapy with bicalutamide, 50 mg orally once daily. After 10 days of antiandrogen therapy, a LHRH agonist (goserelin acetate 10.8 mg subcutaneous depot injection) was administered and continued as monotherapy every 3 months. Intensity-modulated radiotherapy (IMRT) was delivered 45-60 days after initiation of ADT over a period of 4-6 weeks.

Patients who completed 1 year of ADT and had regular follow-up were included in the analysis. Exclusion criteria were known chronic liver disease (including viral hepatitis, alcoholic liver disease, or other chronic hepatic conditions), active malignancies other than prostate cancer, significant alcohol use, prior prostate surgery, history of chemotherapy, and metastatic disease.

MAIN POINTS

- Androgen deprivation therapy (ADT) was associated with a time-dependent increase in FIB-4 scores among patients with prostate cancer.
- No significant changes in FIB-4 scores were observed during the first 6 months of treatment.
- A significant increase in the FIB-4 score was observed at 12 months, suggesting a delayed effect of ADT on liver fibrosis markers.
- Metabolic parameters, including lipid profile and HbA1c, remained stable despite changes in FIB-4 scores.
- These findings underscore the importance of longitudinal monitoring of liver fibrosis markers in patients undergoing long-term ADT.

Data Collection

Demographic characteristics, medical history, and laboratory results of the patients were documented retrospectively. Metabolic and treatment-related laboratory parameters were collected from routine follow-up assessments. To estimate the risk of hepatic fibrosis, FIB-4 index was calculated at baseline and at 6 and 12 months using the following formula: FIB-4 = (Age × AST) / (Platelet count × √ALT). Longitudinal changes in the individual FIB-4 components were assessed at the same time points. FIB-4 values were interpreted according to established cut-off values for advanced fibrosis risk.[13]

Statistical Analysis

Data analyses were carried out using R program (v4.5.0; www.r-project.org) and SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was applied to assess whether continuous data followed a normal distribution. Continuous variables are expressed as mean ± standard deviation or median (Q1-Q3), as appropriate. For comparisons between 2 independent groups, the 2-tailed Mann–Whitney *U*-test was used when the data were non-normally distributed, and the independent samples *t*-test was applied when the data followed a normal distribution. For paired baseline-to-6-month comparisons of triglycerides, LDL-C, HDL-C, HbA1c, PSA, and testosterone, the paired-samples *t*-test or Wilcoxon signed-rank test was used according to the normality of the within-subject differences. For longitudinal comparisons of FIB-4 scores, a Friedman test was performed, followed by Bonferroni-corrected pairwise comparisons, using complete-case analysis. In all longitudinal FIB-4 calculations, age was fixed at the baseline value to eliminate the confounding effect of age increment on the score. Because of the retrospective design, no formal a priori sample size calculation was performed. A post-hoc sensitivity analysis aligned with the repeated-measures design was subsequently conducted based on the complete-case cohort (n = 42), 3 repeated measurements, $\alpha = 0.05$, Cohen's $f = 0.29$, and assuming sphericity ($\varepsilon = 1$), which indicated an estimated statistical power of 82.4% for detecting a moderate longitudinal effect. A *P*-value of < .05 was considered statistically significant for all analyses.

Results

A total of 74 patients were included in the study. Baseline characteristics are summarized in Table 1. The mean age was 66.9 ± 8.5 years, and the mean BMI was 28.5 ± 4.1 kg/m^2. Diabetes mellitus was present in 22 patients (29.7%); among them, 19 (27.1%) were receiving metformin, 1 (1.4%) pioglitazone, 5 (6.8%) sodium–glucose cotransporter-2 (SGLT2) inhibitors, and 11 (14.9%) dipeptidyl peptidase-4 (DPP-4) inhibitors. No new antidiabetic medications or statins were initiated during follow-up. The median prostate volume was 49.0 (38.0-63.2) mL. After LHRH agonist therapy, serum total PSA and total testosterone levels decreased significantly ($P < .001$), confirming effective androgen suppression. In contrast, no significant changes were observed in lipid parameters, including triglycerides, LDL-C, and HDL-C, or in HbA1c levels ($P > .05$) (Table 2).

FIB-4 data were available for 74 patients at baseline, 50 at month 6, and 42 at month 12. At baseline, 55.4% (41/74) of patients had FIB-4 values <1.3, 40.5% (30/74) had values between 1.3 and 2.67, and 4.1% (3/74) had values >2.67. Longitudinal analyses were performed on patients with complete data at all 3 time points (n = 42). Longitudinal changes in FIB-4 and its components (AST, ALT, and platelet count) are presented in Table 3. The Friedman test showed a significant difference in FIB-4 scores across time points ($P = .037$).

Table 1. Baseline Patient Characteristics

	Patients (N = 74)
Age, years	66.9 ± 8.5
BMI, kg/m^2	28.5 ± 4.1
DM, n (%)	22 (29.7)
Metformin, n (%)	19 (27.1)
Pioglitazone, n (%)	1 (1.4)
SGLT2 inhibitor, n (%)	5 (6.8)
DPP-4 inhibitor, n (%)	11 (14.9)
HPL, n (%)	20 (27.4)
Statin, n (%)	22 (29.7)
ACD, n (%)	44 (60.3)
Disease duration, months	24 (12-24)
Prostate volume, mL	49.0 (38.0-63.2)
Pelvic nodal irradiation, n (%)	24 (32.4)
FPG, mg/dL	115.4 ± 31.1
AST (U/L)	20.0 (17.0-25.2)
ALT (U/L)	25.0 (18.0-34.0)
Platelet (×10^3/μL)	220.7±52.9
FIB-4	1.21 (0.99-1.52)

ACD, atherosclerotic cardiovascular disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; FIB-4, fibrosis-4 index; FPG, fasting plasma glucose; HPL, hyperlipidemia; SGLT2, sodium–glucose cotransporter 2.

Bonferroni-corrected pairwise comparisons showed a significant increase in FIB-4 at month 12 compared with baseline (adjusted $P = .036$), whereas no significant difference was observed between baseline and month 6 (adjusted $P = .243$) (Figure 1). Among the 42 patients with complete follow-up, the absolute change in FIB-4 from baseline to month 12 was 0.25 (Q1-Q3: −0.11 to 0.49; 95% CI: 0.07-0.62). Within this cohort, FIB-4 risk category distribution was 57.1% (24/42), 40.5% (17/42), and 2.4% (1/42) at baseline, and 45.2% (19/42), 47.6% (20/42), and 7.1% (3/42) at month 12; 12 patients (28.6%) shifted to a higher FIB-4 risk category, while 6 (14.3%) shifted to a lower category.

To assess potential selection bias due to attrition, baseline demographic and laboratory parameters (age, BMI, presence of DM and hyperlipidemia, AST, ALT, platelet count, and FIB-4) were compared between patients with complete 12-month follow-up (n = 42) and those without (n = 32). No significant differences were observed between the 2 groups (all $P > .05$).

Table 2. Laboratory Parameters Before and After Luteinizing Hormone–Releasing Hormone Agonist Therapy

Parameter	Baseline	After 6 months	*P* value
TG (mg/dL)	126.5 (95.2-183.5)	144.0 (100.7-189.5)	.277
LDL-C (mg/dL)	119.5 (81.5-141.5)	111.0 (81.5-146.5)	.569
HDL-C (mg/dL)	46.0 (39.0-51.5)	48.5 (39.2-53.0)	.139
HbA1c, %	6.5 (5.8-7.5)	6.6 (5.9-7.6)	.062
Total PSA (ng/mL)	9.00 (5.40-17.10)	0.02 (0.01-0.12)	**<.001**
Total Testosterone (ng/dL)	467.5±238.3	18.5±9.4	**<.001**

Bold values indicate statistical significance ($P < .05$).
HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LHRH, luteinizing hormone–releasing hormone;, PSA, prostate-specific antigen; TG, triglycerides.

Discussion

In this study, temporal changes in FIB-4 scores were evaluated in patients with prostate cancer receiving LHRH agonist therapy, and a significant increase was observed at 12 months. Although early changes at 6 months did not reach statistical significance, a time-dependent pattern emerged, suggesting a cumulative effect of ADT on liver fibrosis markers. Androgen deprivation therapy is known to induce metabolic alterations, including insulin resistance, increased fat mass, and adverse lipid changes, all of which contribute to metabolic dysfunction. These changes are thought to play a central role in the development of MASLD.[8,9,15] Previous studies have demonstrated an association between low testosterone levels and hepatic steatosis, suggesting a mechanistic link between androgen deficiency and hepatic alterations.[16-18] Consistent with this, population-based studies in patients with prostate cancer have reported an increased risk of liver-related outcomes among those receiving ADT.[8]

Importantly, while most previous studies have focused on hepatic steatosis, the present findings suggest that the impact of ADT may extend beyond steatosis to include early fibrotic changes. To the authors' knowledge, longitudinal data evaluating noninvasive fibrosis markers in this context are limited, and the observed time-dependent increase in FIB-4 scores provides novel evidence supporting a potential role for ADT in fibrosis progression. This distinction is clinically relevant, as fibrosis stage rather than steatosis is the primary determinant of long-term hepatic and cardiovascular outcomes.[12,19] The observed delayed increase in FIB-4 scores may indicate that fibrosis-related changes develop gradually over time, rather than occurring in the early phases of treatment. Mechanistically, hepatic stellate cells, the principal effector cells of liver fibrosis, predominantly express estrogen receptor 1 rather than the androgen receptor; sex hormone depletion has been shown to exacerbate liver fibrosis in animal models, an effect mitigated by estradiol replacement, suggesting that reduced aromatization of testosterone to estradiol may contribute to hepatic stellate cell activation during ADT.[20] However, evidence regarding the direct effects of androgens on liver fibrosis remains inconsistent across experimental models, and the precise mechanism linking ADT to fibrogenesis warrants further investigation.[21]

Notably, no single component of the FIB-4 score appeared to fully account for the observed increase, suggesting that the findings reflect a composite change rather than an isolated alteration in aminotransferases or platelet count. Although a subset of patients shifted to a higher FIB-4 risk category at month 12, the absolute number affected remained small, and the clinical significance of these categorical shifts should be interpreted cautiously, given the limited sample size. Furthermore, given the relatively advanced mean age of our cohort, the standard FIB-4 risk thresholds applied in this study may not fully account for age-related elevations in FIB-4 reported in older populations, for whom higher cut-off values have been proposed.[13]

Interestingly, despite the known metabolic effects of ADT, we did not observe significant changes in lipid parameters in the cohort. This finding suggests that the increase in FIB-4 may not be fully explained by conventional metabolic parameters and may reflect

Table 3. Longitudinal Changes in FIB-4 Components and FIB-4 Score (n = 42)

	Baseline	Month 6	Month 12	*P*
AST (U/L)	19.0 (16.0-22.0)	21.5 (17.0-28.0)	20.0 (17.5-26.0)	**.005**[a]
ALT (U/L)	22.0 (17.5-31.0)	23.0 (18.5-31.3)	20.0 (15.8-31.0)	.595[a]
Platelet (×10^3/μL)	230.8±58.0	233.8±52.2	227.5±52.2	.652[b]
FIB-4	1.21 (0.93-1.49)	1.29 (1.05-1.73)	1.42 (1.00-1.84)	**.037**[a]

AST, aspartate aminotransferase; ALT, alanine aminotransferase; FIB-4, fibrosis-4 index.
[a]Friedman test. Bonferroni-corrected pairwise comparisons: AST—baseline vs. month 6: adjusted *P* = .007, baseline vs. month 12: adjusted *P* = .036; FIB-4—baseline vs. month 6: adjusted *P* = .243, baseline vs. month 12: adjusted *P* = .036.
[b]Repeated-measures ANOVA. Mauchly's test indicated sphericity was met (W = 0.947, *P* = .337). Bonferroni-corrected pairwise comparisons revealed no significant differences between any time points (all *P* = 1.000).

more complex mechanisms, including androgen deficiency–related alterations in hepatic metabolism and inflammation. Furthermore, a subset of patients in the cohort were receiving medications with potential favorable hepatic effects, including pioglitazone, SGLT2 inhibitors, and statins;[22-24] however, the number of patients receiving pioglitazone (n = 1) or SGLT2 inhibitors (n = 4) within the complete-case cohort was too small. Nonetheless, no new antidiabetic or lipid-lowering medications were initiated during the follow-up period.

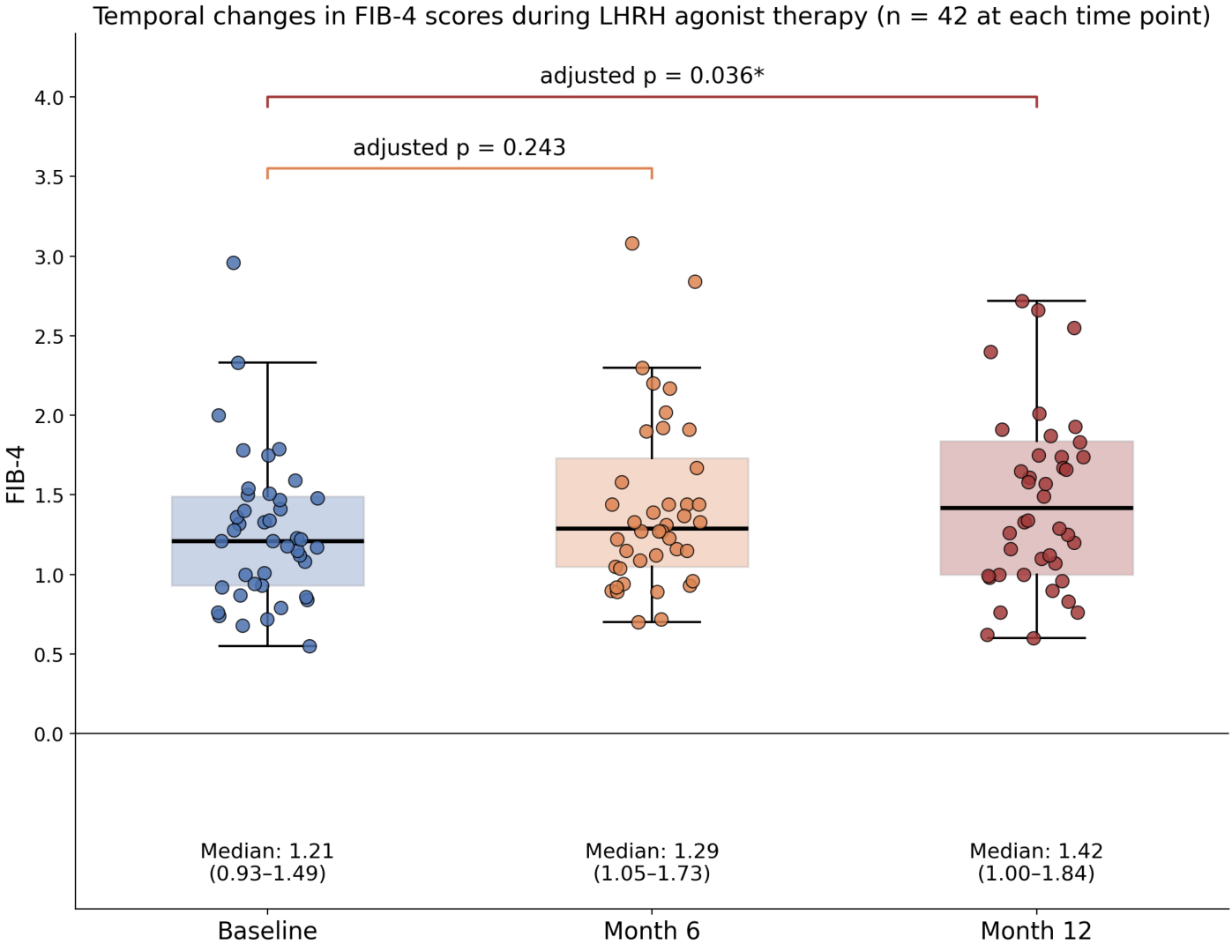

Figure 1. Temporal changes in FIB-4 scores during luteinizing hormone–releasing hormone agonist therapy. Boxplots show median and 25th-75th percentile FIB-4 values at baseline, month 6, and month 12 (n = 42 at each time point). A Friedman test showed a significant difference across time points (*P* = .037); Bonferroni-corrected pairwise comparisons versus baseline are shown above the plot (month 6, adjusted *P* = .243; month 12, adjusted *P* = .036). FIB-4, fibrosis-4 index; LHRH, luteinizing hormone–releasing hormone.

It is clear that prospective studies with larger participants in this patient population are needed to more definitively exclude a potential confounding effect of these medications on FIB-4 trajectories. Beyond pharmacological factors, non-pharmacological contributors also warrant consideration. Although all patients received pelvic radiotherapy, with a subset (32.4%) additionally receiving pelvic nodal irradiation, the liver lies outside the standard radiation field in prostate cancer and is not considered an organ at risk in this setting. Clinically significant hepatic radiation exposure is therefore unlikely, making radiotherapy an improbable contributor to the observed FIB-4 changes.[25] However, in the absence of a non-ADT comparator group, we cannot entirely exclude a contribution from aging or cancer-related metabolic changes to the observed FIB-4 trajectory.

This study has several limitations. First, the retrospective, single-center design may limit the generalizability of the findings. Second, the decrease in sample size during follow-up—reflecting the unavailability of 1 or more FIB-4 components (AST, ALT, or platelet count) at routine clinical assessment rather than missed clinic visits—may have reduced the ability to detect smaller longitudinal changes, despite adequate power for moderate effects. Importantly, baseline comparisons between patients with and without complete 12-month follow-up revealed no significant differences in demographic, clinical, or hepatic parameters, suggesting that missingness was unrelated to baseline disease severity and unlikely to have introduced substantial selection bias. Nevertheless, the possibility of unmeasured confounding due to attrition cannot be entirely excluded. Third, the use of a noninvasive fibrosis marker rather than histological confirmation is an inherent limitation. In addition, elastography-based assessments were not available because of the retrospective nature of the study. However, FIB-4 is a widely validated and clinically relevant tool for fibrosis risk assessment, making it suitable for longitudinal evaluation in real-world settings.[13,26]

Androgen deprivation therapy may be associated with a time-dependent increase in noninvasive liver fibrosis markers, as reflected by rising FIB-4 scores at 12 months. The observed increase in FIB-4 scores underscores the importance of liver health monitoring in patients receiving ADT, particularly in those undergoing prolonged therapy. Further prospective studies with larger cohorts and longer follow-up are needed to clarify the clinical significance of these findings and to determine whether ADT contributes to progressive liver fibrosis.

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

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approved by the Acıbadem Ankara University Ethics Committee (Decision number: 2025-05/23, Date: March 20, 2025).

Informed Consent: Informed consent was obtained from the patients who agreed to take part in the study.

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