Dicle Tıp Dergisi / Dicle Med J (2026) 53 (1) : 159-168

www.diclemedj.org

Original Article / Özgün Araştırma

Histopathological Evaluation and Treatment Necessity in Patients with Immune-Tolerant, Inactive, and Gray-Zone Chronic Hepatitis B

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Received: 01.12.2025; Revised: 01.03.2026; Accepted: 03.03.2026

Abstract

Objective: To evaluate the need for antiviral therapy in chronic hepatitis B (CHB) patients with normal ALT levels who are HBeAg-positive (Immune tolerant phase), HBeAg-negative (Inactive phase), or in the gray-zone, by assessing liver fibrosis stage and histological activity index (HAI).

Methods: This retrospective cross-sectional study included 36 immune-tolerant HBeAg-positive, 21 inactive HBeAg-negative, and 193 gray-zone CHB patients without prior antiviral therapy. The inactive phase was defined as persistently normal ALT and HBV DNA <2000 IU/mL, while patients with normal ALT but HBV DNA ≥2000 IU/mL were classified as gray-zone. Liver biopsies were evaluated using HAI and the Ishak fibrosis scoring system. Antiviral therapy indication was defined as fibrosis stage ≥2 and/or HAI ≥6.

Results: A total of 250 patients (mean age 44.2 ± 12.2 years; 44.4% male) were analyzed. Of these, 14.4% were immune-tolerant and 85.6% were in inactive/gray-zone phases. Among inactive/gray-zone patients, HBV DNA was <2000 IU/mL in 9.8% and ≥2000 IU/mL in 90.2%. Overall, 37.6% (94/250) met antiviral therapy criteria, including 41.6% of immune-tolerant, 33.3% of inactive, and 37.3% of gray-zone patients.

Conclusion: A notable proportion of CHB patients with normal ALT show histological evidence warranting antiviral therapy. These results emphasize that phase classification at a single time point is inadequate; dynamic and comprehensive evaluation is essential.

Keywords: Hepatitis B, inactive phase, immune-tolerant phase, gray-zone, fibrosis, antiviral therapy

DOI: 10.5798/dicletip.1906472

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Kronik Hepatit B'de Sessiz Tehdit: İmmün Toleran, İnaktif ve Gri Zon Fazlarında Gizli Fibrozis ve Tedavi Endikasyonları

Öz

Amaç: ALT düzeyleri normal olan kronik hepatit B (KHB) hastalarında — HBeAg pozitif (immün toleran faz), HBeAg negatif (inaktif faz) veya gri zon fazında bulunan olgularda — karaciğer fibrozis evresi ve histolojik aktivite indeksi (HAI) değerlendirilerek antiviral tedavi gereksiniminin belirlenmesi amaçlanmıştır.

Yöntemler: Bu retrospektif kesitsel çalışmada, daha önce antiviral tedavi almamış 36 immün toleran HBeAg pozitif, 21 inaktif HBeAg negatif ve 193 gri zon KHB hastası incelendi. İnaktif faz, sürekli normal ALT ve HBV DNA <2000 IU/mL olarak tanımlanırken, ALT normal fakat HBV DNA ≥2000 IU/mL olan hastalar gri zon olarak sınıflandırıldı. Karaciğer biyopsileri HAI ve Ishak fibrozis skorlama sistemi ile değerlendirildi. Tedavi endikasyonu fibrozis evresi ≥2 ve/veya HAI ≥6 olarak kabul edildi.

Bulgular: Toplam 250 hasta (ortalama yaş 44,2 ± 12,2 yıl; %44,4 erkek) çalışmaya dahil edildi. Hastaların %14,4'ü immün toleran, %85,6'sı inaktif/gri zon fazdaydı. Genel olarak, %37,6'sı (94/250) antiviral tedavi kriterlerini karşıladı.

Sonuç: Normal ALT düzeyine rağmen birçok KHB hastasında antiviral tedavi gereksinimi bulunmaktadır. Bu durum, KHB'nin dinamik doğasını ve faz sınıflandırmasının tek bir zaman noktasına göre yetersizliğini göstermektedir.

Anahtar kelimeler: Hepatit B, inaktif faz, immün toleran faz, gri zon, fibrozis, antiviral tedavi.

INTRODUCTION

Chronic hepatitis B (CHB) remains a significant global health problem. According to the World Health Organization, approximately 300 million people are currently infected with HBV[1]. Persistent HBV infection is a leading cause of complications such as cirrhosis and hepatocellular carcinoma (HCC)[2]. The natural course of HBV infection consists of distinct clinical phases, including immune-tolerant, immune-active, inactive carrier, and reactivation. These phases are critical for assessing disease progression and guiding treatment decisions[3].

The immune-tolerant phase is typically observed in young patients, particularly in East Asian populations, and is characterized by high HBV DNA levels, HBeAg positivity, and persistently normal ALT levels. In contrast, the inactive phase is defined by HBeAg negativity, persistently normal ALT, and HBV DNA <2000 IU/mL[4].

However, some patients do not fully fit these classic definitions and are classified into an "indeterminate (gray) zone." These patients are HBeAg-negative, have HBV DNA ≥2000 IU/mL, and normal ALT levels. Clinically, they are often considered inactive carriers; however, liver biopsy and non-invasive assessments have shown that this group may develop silent but progressive liver injury[5,6]. Therefore, management decisions based solely on ALT levels may be insufficient.

In HBeAg-negative patients with normal ALT levels, the following criteria suggest the need for antiviral therapy: HBV DNA ≥2000 IU/mL, fibrosis stage ≥F2 (assessed by biopsy or FibroScan), high scores on non-invasive scoring systems (e.g., FIB-4, APRI), and a family history of cirrhosis or HCC. Patients exhibiting these features should be considered candidates for antiviral treatment.

Current clinical guidelines do not recommend antiviral therapy for patients in the immune-tolerant or inactive/gray-zone phases; instead, they advise regular monitoring including ALT levels, HBV DNA, and non-invasive fibrosis assessments. This approach has been maintained in recent updates by the European

Association for the Study of the Liver (EASL) and the World Health Organization (WHO)[7].

This study aims to re-evaluate the need for antiviral therapy in patients classified as immune-tolerant, inactive, or gray-zone, and to discuss the findings in the context of current guidelines and the existing literature.

METHODS

Study Population

This retrospective cross-sectional study included 250 HBsAg-positive patients who underwent ultrasound-guided liver biopsy at our tertiary care center between January 2007 and January 2018. Patients who had not received prior antiviral therapy were included in the final analysis. Clinical and laboratory data were retrospectively extracted from electronic medical records.

Definitions and Patient Classification

Patients were classified into immune-tolerant, inactive, and "gray-zone" phases in accordance with the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) and the clinical practice guidelines[2,3].

Persistently Normal ALT: Defined as consistently normal alanine aminotransferase (ALT) levels (<32 IU/L) across at least three measurements over a 6-month follow-up period.

Gray-Zone Definition: Patients were categorized as being in the gray-zone if they presented with HBV DNA levels ≥ 2,000 IU/mL but did not meet the criteria for immune-active phase (normal ALT, no clinical evidence of advanced liver disease), or based on the criteria outlined in the updated AASLD guidelines for intermediate-phase monitoring[2].

Diagnostic Approach and Limitations

In this study, ultrasound-guided liver biopsy served as the primary diagnostic tool to evaluate hepatic fibrosis and inflammation. While non-invasive markers such as FibroScan, FIB-4, or APRI are valuable, this study focused on histopathological findings as the definitive gold standard. [Optional: The retrospective nature of the study limited the availability of comprehensive parameters for calculating non-invasive scores across all patients, therefore histopathology was prioritized.

Exclusion Criteria

Patients with other chronic viral hepatitis (HCV, HDV, HIV), hepatocellular carcinoma (HCC), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD; diagnosed via clinical, laboratory, and ultrasound criteria), autoimmune hepatitis, hereditary liver diseases (e.g., Wilson's disease, hemochromatosis), drug-induced liver injury, hepatobiliary malignancies, or a history of organ transplantation were excluded. The exclusion process is summarized in Table I.

Figure I: Exclusion Flowchart of the Study Population

Study Step	Details	Patients (n)
Initial assessment	Patients with a history of liver biopsy were evaluated.	1,039
↓	Exclusion 1: Toxic hepatitis (n=21), NASH (n=73), HCC (n=16), Other viral infections (n=19)	129 excluded
↓	Remaining patients with HBV infection	910
↓	Exclusion 2: Incomplete data (n=33), Lost to follow-up (n=62)	95 excluded
↓	Immune-active patients excluded	436 excluded
↓	Immune-tolerant/inactive HBV patients with ALT >32 IU/L excluded	129 excluded
↓	Final study population included	250

HBV – Hepatitis B virus; NASH – Non-alcoholic steatohepatitis; HCC – Hepatocellular carcinoma; ALT – Alanine aminotransferase.

Liver Biopsy and Histological Assessment

Liver histopathology was evaluated using the Ishak scoring system, which includes two main parameters: the Histological Activity Index (HAI) to assess necroinflammatory activity and the Ishak fibrosis score to determine the degree of fibrosis. Patients were classified into three groups—immune-tolerant, inactive carrier, and

gray-zone—based on their histopathological and biochemical characteristics.

In this study, indication for antiviral therapy was defined in accordance with international guidelines as HAI ≥6 and/or fibrosis stage ≥2. This retrospective study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine (Approval Date: 30.04.2025; Approval No: 458).

Statistical Analysis

Descriptive statistics for continuous variables were presented as median (25th–75th percentile) and minimum–maximum values. Categorical variables were summarized as frequencies and percentages.

The association between categorical variables and the need for antiviral therapy was analyzed using the Chi-square test. Differences in continuous variables according to therapy requirement were evaluated with the Mann–Whitney U test due to non-normal distribution.

All analyses were performed using IBM SPSS Statistics version 25. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 1,039 patients with chronic hepatitis B (CHB) who had undergone liver biopsy were initially evaluated. Following the application of exclusion criteria, 250 patients were included in the final analysis. The mean age was 44.2 ± 12.2 years (range: 18–73), and the cohort comprised 44.4% males and 55.6% females. Overall, antiviral treatment indication was identified in 37.6% of patients, primarily based on fibrosis stage ≥2 and/or HAI ≥6 (Table 2).

Regarding clinical phase distribution, 14.4% of patients were in the immune-tolerant phase (HBeAg-positive), whereas 85.6% were classified as being in the inactive or gray-zone phase. Notably, the majority of patients (90.2%) had HBV DNA levels ≥2000 IU/mL and were thus considered within the "gray-zone" category.

Table I: Distribution of Descriptive and Quantitative Characteristics of the Study Population (n=250)

Characteristic / Parameter	n (%) / Median (Q1–Q3)	Min–Max
Age <40 / ≥40 (years)	93 (37.2) / 157 (62.8)	—
Gender (Female / Male)	139 (55.6) / 111 (44.4)	—
HBeAg status (Neg / Pos)	214 (85.6) / 36 (14.4)	—
Phase (Immune-tolerant / Inactive-gray)	36 (14.4) / 214 (85.6)	—
HBV DNA (Inactive / Gray-zone)	<2000: 21 (9.8) / ≥2000: 193 (90.2)	—
Treatment indication (No / Yes)	156 (62.4) / 94 (37.6)	—
PT (sec)	13.1 (11.7–14.5)	9.5–1105
AST (U/L)	21 (18–24.93)	8–1301
ALT (U/L)	21 (16.4–26)	5.3–3001
PLT (×10⁹/L)	235 (198–274)	100–461
HBV DNA (IU/mL)	12,000 (3763–50,928)	18–190,000,000
HBsAg (IU/mL)	2,841 (1901–4212)	72–20,013
HAI score	5 (3–6)	1–16
Fibrosis score	2 (2–2)	0–5

Q1–Q3 = 25th–75th percentiles; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; PLT, platelet count; PT, prothrombin time; HAI, histologic activity index.

Aminotransferase; ALT = Alanine Aminotransferase; PLT = Platelet; HBV DNA = Hepatitis B Virus DNA; HBsAg = Hepatitis B Surface Antigen; HAI = Histological Activity Index

In the overall cohort, fibrosis stage 5 (Ishak system; consistent with advanced fibrosis/cirrhosis) was identified in 2 patients in the immune-tolerant phase, 2 patients in the inactive phase, and 6 patients in the gray-zone phase. Given that these cases represented only a very small proportion of the total cohort, their impact on the statistical analyses was considered negligible (Table 3).

Table II: Distribution of patients with fibrosis stage 5 (consistent with cirrhosis) across immune-tolerant, inactive, and gray-zone phases

Phase	Patients	Fibrosis Score 5 (Cirrhosis)	Percentage (%)	Note
Immune-tolerant	36	2	5.6	No statistical analysis performed
Inactive phase	21	2	9.5	No statistical analysis performed
Gray-zone	193	6	3.1	No statistical analysis performed
Total	250	10	4.0	No statistical analysis performed

When treatment requirements were evaluated according to clinical phases: Immune-Tolerant Phase (n = 36)

By age group, treatment indication was identified in 40.7% of patients aged <40 years and in 44.4% of those aged ≥40 years, with no significant difference between groups (p = 0.85). The proportion was 44.1% among males and 31.4% among females (p = 0.09). Overall, 15 of the 36 patients (41.6%) in the immune-tolerant phase met treatment criteria.

Patients with treatment indication had significantly higher HAI [6 (5–9) vs. 3 (2–4.5)] and fibrosis scores [3 (2–4) vs. 2 (1–2)] compared to those without indication (both p < 0.001). No significant differences were observed in biochemical parameters (PT, AST, ALT, PLT, HBV DNA, HBsAg) between groups (all p > 0.05) (Table 4).

Table III: Evaluation of clinical and laboratory characteristics by treatment requirement in immune-tolerant patients (n = 36)

Characteristic	No treatment needed (n = 21)	Treatment needed (n = 15)	p value
Age <40 / ≥40 (years)	16 (59.3) / 5 (55.6)	11 (40.7) / 4 (44.4)	0.85†
Gender (Male / Female)	8 (44.4) / 13 (72.2)	10 (55.6) / 5 (27.8)	0.09†
PT (sec)	12.9 (11.95–14.15)	13.6 (12.7–14.2)	0.30‡
AST (U/L)	24 (20–28.87)	25.5 (23.5–28.5)	0.23‡
ALT (U/L)	28 (16.91–29.8)	26 (23.1–29.6)	0.68‡
PLT (×10⁹/L)	269 (211–314)	232 (190–264)	0.13‡
HBV DNA (IU/mL)	10,000,000 (114,000–170,000,000)	250,000 (15,900–54,780,356)	0.14‡
HBsAg (IU/mL)	1241 (364.3–1937.5)	2014 (1099.3–2356)	0.10‡
HAI score	3 (2–4.5)	6 (5–9)	<0.001‡
Fibrosis score	2 (1–2)	3 (2–4)	<0.001‡

Q1–Q3: 25th–75th percentile; † Chi-square test; ‡ Mann–Whitney U test; p < 0.05 was considered statistically significant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; PLT, platelet count; PT, prothrombin time; HAI, histologic activity index.

Inactive Phase, HBV DNA <2000 IU/mL (n = 21)

According to age distribution, treatment indication was observed in 25.0% of patients

aged <40 years and in 35.3% of those aged ≥40 years, with no statistically significant association between age and treatment requirement (p = 0.69). The proportion was 38.5% among males and 25.0% among females (p = 0.09). Overall, 7 of the 21 patients (33.3%) in the inactive phase met treatment criteria.

Histopathological assessment revealed significantly higher HAI [6 (5.25–11.5) vs. 3 (2–4.5); p = 0.001] and fibrosis scores [2.5 (2–5) vs. 1 (1–2); p = 0.004] in patients with treatment indication compared to those without. No significant differences were identified in biochemical parameters (ALT, AST, PT, PLT, HBV DNA, HBsAg) between groups (all p > 0.05) (Table 5).

Table IV: Evaluation of clinical, biochemical, and histopathological characteristics based on treatment requirement in inactive phase patients with HBV DNA <2000 IU/mL

Characteristic	No treatment needed (n = 14)	Treatment needed (n = 7)	p value
Age <40 / ≥40 (years)	3 (75) / 11 (64.7)	1 (25) / 6 (35.3)	0.69†
Gender (Male / Female)	8 (61.5) / 6 (75)	5 (38.5) / 2 (25)	0.09†
PT (sec)	12.7 (11.2–13.9)	12.2 (11.4–13.2)	0.79‡
AST (U/L)	20.2 (18.4–23)	17.9 (12.8–20.5)	0.17‡
ALT (U/L)	21 (15.1–26.3)	17.5 (12.5–30.5)	0.71‡
PLT (×10⁹/L)	198 (179.5–261)	206.5 (145.5–266.8)	0.82‡
HBV DNA (IU/mL)	215 (148–362)	401 (69.5–1165)	0.94‡
HBsAg (IU/mL)	3119 (2276.5–4112)	2352.9 (2069.3–3084)	0.18‡
HAI score	3 (2–4.5)	6 (5.25–11.5)	0.001‡
Fibrosis score	1 (1–2)	2.5 (2–5)	0.004‡

Q1–Q3: 25th–75th percentile; † Chi-square test; ‡ Mann–Whitney U test; p < 0.05 considered statistically significant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; PLT, platelet count; PT, prothrombin time; HAI, histologic activity index.

Gray-Zone Phase, HBV DNA ≥2000 IU/mL (n = 193)

By age group, treatment indication was present in 22.6% of patients aged <40 years and in 44.3% of those aged ≥40 years, with a statistically significant difference between groups (p = 0.004). The proportion was 45.0% among males and 31.9% among females; however, this difference did not reach statistical significance (p = 0.07). Overall, 72 of the 193 patients (37.3%) in the gray-zone phase met treatment criteria.

Histopathological evaluation demonstrated significantly higher HAI and fibrosis scores in patients with treatment indication compared to those without. Among biochemical parameters, only AST levels differed significantly, while all other markers were comparable between groups (Table 6).

Table V: Comparison of Clinical, Biochemical, and Histopathological Characteristics According to Treatment Requirement in Gray-Zone Phase Patients with HBV DNA ≥2000 IU/mL (n=193)

Characteristic	No Treatment Needed (n=121)	Treatment Needed (n=72)	p value
Age, n (%)			0.004†
< 40 years	48 (77.4)	14 (22.6)	
≥ 40 years	73 (55.7)	58 (44.3)	
Gender, n (%)			0.07†
Male	44 (55.0)	36 (45.0)	
Female	77 (68.1)	36 (31.9)	
PT (sec), Median (Q1–Q3)	13.2 (11.6–14.8)	13.2 (11.8–14.6)	0.91‡
AST, Median (Q1–Q3)	20 (17–22.2)	21.3 (18–27.7)	0.01‡
ALT, Median (Q1–Q3)	19.6 (15.4–24)	20.3 (16–25.2)	0.60‡
PLT, Median (Q1–Q3)	234.5 (204–273.7)	240 (186–266.7)	0.44‡
HBV DNA, Median (Q1–Q3)	13867.5 (4905–38000)	6844.5 (3742.3–35596.3)	0.09‡
HBsAg, Median (Q1–Q3)	3307.5 (2053.5–4566.3)	3247.3 (2149.1–447.2)	0.67‡
HAI Score, Median (Q1–Q3)	4 (3–5)	6 (5.3–7)	< 0.001‡
Fibrosis Score, Median (Q1–Q3)	2 (1.3–2)	3 (2–3)	< 0.001‡

Chi-square test; ‡ Mann–Whitney U test. p < 0.05 was considered statistically significant. HBV DNA: Hepatitis B virus DNA; HBsAg: Hepatitis B surface antigen; PT: Prothrombin time; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PLT: Platelet count; HAI: Histologic activity index

DISCUSSION

This retrospective cross-sectional study was conducted in the Department of Gastroenterology, based on liver biopsies performed under ultrasound guidance in patients with immune-tolerant, inactive chronic hepatitis B (CHB), and gray-zone phases

The age and sex distribution of our 250-patient cohort was consistent with existing literature. Notably, 37.6% of our patients met the criteria for antiviral treatment (HAI ≥ 6 and/or fibrosis ≥ 2), suggesting that the immune-tolerant, inactive, and gray-zone phases may not always follow a clinically silent course.

Our findings indicate that clinical decisions should not rely solely on classical biochemical parameters. We observed a significantly higher treatment requirement in gray-zone patients aged ≥ 40 years (p=0.004), reinforcing age as a critical determinant of disease progression due to cumulative hepatocellular injury and declining immune responsiveness[8–10]. While sex did not show a statistically significant difference regarding treatment needs (p=0.07), the observed trends align with previous data.

Histopathological analysis revealed that patients meeting treatment criteria exhibited significantly higher HAI and fibrosis scores, even within low-viremia groups. This underscores the limitations of using HBV DNA levels alone for clinical decision-making. Furthermore, the presence of significant histological damage in HBeAg-negative patients with normal ALT confirms that "silent" phases may harbor progressive inflammatory processes[5,11–14]. We also identified AST levels as a potentially superior marker for fibrosis progression compared to ALT, likely due to its sensitivity to mitochondrial damage[15].

Current international guidelines, such as those from the EASL and AASLD, often adopt a "watch-and-wait" strategy for these phases[2,3]. However, our data suggest this approach may be insufficient for a subset of patients. The variability in ALT upper limit of normal (ULN) thresholds—ranging from 25–40 IU/L across different global guidelines—complicates

management[17,18]. By adopting a local ULN of 32 IU/L derived from the Turkish population, our study provides a more objective assessment aligned with local epidemiological evidence[19,20].

Limitations of the Study

This study has several limitations: its retrospective and single-center design may restrict the generalizability of the findings. Additionally, liver biopsy, while the gold standard, is subject to sampling errors and inter-observer variability. The lack of standardized definitions for CHB phases across international guidelines may introduce heterogeneity. Finally, the use of biochemical parameters at single time points prevents an assessment of long-term dynamic changes, and the limited number of patients with advanced fibrosis may have constrained the statistical power of subgroup analyses.

Strengths of the Study

Despite these limitations, this study provides significant value by focusing on the often-underrepresented immune-tolerant, inactive, and gray-zone phases. The use of histopathological confirmation for all subjects offers a level of precision that complements standard biochemical and virological assessments. By providing a multidimensional evaluation of treatment indications, our study offers real-world data that supports the need for more personalized clinical management.

CONCLUSION

In conclusion, a substantial proportion of patients currently classified in the "non-treatment" phases of CHB exhibit significant histological indications for antiviral therapy. Our results demonstrate that neither HBV DNA nor ALT levels are sufficient as independent markers for disease monitoring. We advocate for a more individualized approach to CHB management, where histopathological or advanced non-invasive assessment is prioritized to identify patients at risk of silent fibrosis progression. These findings provide clinically relevant insights that may inform future updates to international management guidelines.

Abbreviations

AASLD: American Association for the Study of Liver Diseases

ALT: Alanine aminotransferase

APASL: Asian Pacific Association for the Study of the Liver

APRI: Aspartate aminotransferase to platelet ratio index

AST: Aspartate aminotransferase

EASL: European Association for the Study of the Liver

FIB-4: Fibrosis-4 score

HAI: Histologic Activity Index

HBV: Hepatitis B virus

HBeAg: Hepatitis B e antigen

HBsAg: Hepatitis B surface antigen

HBV DNA: Hepatitis B virus deoxyribonucleic acid

HCC: Hepatocellular carcinoma

HDV: Hepatitis D virus

HIV: Human immunodeficiency virus

IU/mL: International units per milliliter

JSG: Japan Society of Gastroenterology

KHB: Chronic Hepatitis B

PLT: Platelet count

PT: Prothrombin time

SUT: Sağlık Uygulama Tebliği (Turkish National Health Reimbursement Code)

WHO: World Health Organization

Data Availability Statement: The datasets generated and/or analyzed during the current study

are available from the corresponding author on reasonable request.

Ethical Approval: This retrospective study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine (Approval Date: 30.04.2025; Approval No: 458).

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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