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# Immune Reconstitution Inflammatory Syndrome in Patients with Human Immunodeficiency Virus Infection: A Multicenter BUHASDER Study

HIV Enfekte Hastalarda İmmün Rekonstitüsyon İnflamatuvar Sendromu: Çok Merkezli Bir BUHASDER Çalışması

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## Abstract

**Introduction:** The advent of effective antiretroviral therapy (ART) has markedly improved the survival and quality of life of people living with human immunodeficiency virus (HIV). Nevertheless, the rapid restoration of immune function following ART initiation can precipitate immune reconstitution inflammatory syndrome (IRIS), a condition that may lead to clinical deterioration. This study aimed to characterize the clinical features, therapeutic approaches, and outcomes of patients with HIV infection who developed IRIS.

**Materials and Methods:** This retrospective multicenter study included 13 centers. Data from 31 patients with HIV infection diagnosed with immune IRIS were collected from electronic medical records and analyzed. Demographic characteristics, immunologic and virologic status at ART initiation, IRIS type, associated opportunistic infections, treatment strategies, and clinical outcomes were evaluated. In addition, the clinical and laboratory characteristics of survivors (n=26) and non-survivors (n=5) were compared. A p value < 0.05 was considered statistically significant.

**Results:** The mean age of patients at ART initiation was  $42.74 \pm 12$  years (median, 43 years; range, 18-61 years). Twenty-one patients (67.7%) developed paradoxical IRIS, whereas 10 (32.3%) developed unmasking IRIS. The most common OIs were *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, and cytomegalovirus disease. At ART initiation, 71% of patients had a CD4+ T-cell count < 100 cells/mm<sup>3</sup>, and 74% had an HIV RNA level >100,000 IU/mL. In the exploratory mortality analysis, central nervous system (CNS) involvement (p=0.001), progressive multifocal leukoencephalopathy (PML) (p=0.012), lymphoma (p=0.020), meningismus (p=0.048), and worsening cerebrospinal fluid findings (p=0.012) were more frequently observed among non-survivors, as was a higher baseline lymphocyte count at ART initiation (median, 1,640 vs. 870 cells/mm<sup>3</sup>; p=0.036).

**Conclusion:** Most patients who developed IRIS had advanced immunosuppression and a high baseline viral load at ART initiation. CNS involvement and PML were more frequently observed among non-survivors; however, given the small number of deaths, these findings are hypothesis-generating and require confirmation in larger multicenter studies.

**Keywords:** HIV infection, paradoxical IRIS, unmasking IRIS

## Öz

**Giriş:** Antiretroviral tedavinin (ART) kullanıma girmesi, insan immün yetmezlik virüsü (HIV) ile yaşayan bireylerin yaşam süresi ve yaşam kalitesini belirgin şekilde artırmıştır. Bununla birlikte, ART başlanmasını takiben immün fonksiyonların hızlı şekilde yeniden kazanılması, klinik kötüleşmeye yol açabilen immün rekonstitüsyon inflamatuvar sendromunu (IRIS) tetikleyebilmektedir. Bu çalışmanın amacı, IRIS gelişen HIV enfekte hastaların klinik özelliklerini, tedavi yaklaşımlarını ve sonuçlarını değerlendirmektir.

**Gereç ve Yöntemler:** Bu retrospektif çok merkezli çalışmaya 13 merkez katıldı. IRIS tanısı alan 31 HIV ile enfekte hastanın verileri elektronik hasta kayıtlarından elde edilerek analiz edildi. Demografik özellikler, ART başlangıcındaki immünolojik ve virolojik durum, IRIS tipi, eşlik eden fırsatçı enfeksiyonlar, tedavi yaklaşımları ve klinik sonuçlar değerlendirildi. Ayrıca, IRIS gelişikten sonra yaşayan 26 hasta ile ölen 5 hastanın klinik ve laboratuvar özellikleri karşılaştırıldı. İstatistiksel anlamlılık düzeyi p < 0,05 olarak kabul edildi.

**Bulgular:** IRIS gelişen HIV ile enfekte hastaların ART başlangıcındaki ortalama yaşı  $42,74 \pm 12$  yıl (medyan: 43; minimum-maksimum: 18-61) idi. Olguların 21'inde (%67,7) paradoksal, 10'unda (%32,3) ise maskelenmemiş IRIS gelişti. En sık görülen fırsatçı enfeksiyonlar *Mycobacterium tuberculosis*, *Pneumocystis jirovecii* ve sitomegalovirüs hastalığı idi. Hastaların %71'inde ART başlangıcında CD4+ T lenfosit sayısı <100 hücre/mm<sup>3</sup>, %74'ünde ise HIV RNA düzeyi >100,000 IU/mL olarak saptandı. Tanımlayıcı mortalite analizinde santral sinir sistemi (SSS) tutulumu (p = 0,001), progresif multifokal lökoensefalopati (PML) (p = 0,012), lenfoma (p = 0,020), menenjismus (p = 0,048) ve kötüleşen beyin omurilik sıvısı bulguları (p = 0,012) ölen hastalarda daha sık gözlemlendi; benzer şekilde ART başlangıcındaki lenfosit sayısı da ölen hastalarda daha yüksekti (medyan: 1640'a karşı 870 hücre/mm<sup>3</sup>, p = 0,036).

**Sonuç:** Bu çalışmada IRIS gelişen hastaların büyük çoğunluğunda ART başlangıcında ileri derecede immünsüpresyon ve yüksek viral yük bulunduğu gösterildi. SSS tutulumu ve PML ölen hastalarda daha sık gözlemlendi; ancak ölüm sayısının azlığı nedeniyle bu bulgular hipotez oluşturunucudur ve daha geniş çok merkezli çalışmalarda doğrulanmalıdır.

**Anahtar Kelimeler:** HIV enfeksiyonu, paradoksal IRIS, maskelenmemiş IRIS

## Introduction

The use of antiretroviral therapy (ART) induces both quantitative and qualitative changes in the immune response, significantly improving survival rates and quality of life among individuals living with human immunodeficiency virus (HIV)<sup>[1]</sup>. A rapid decline in HIV RNA levels and swift immune reconstitution can, however, lead to the development of immune reconstitution inflammatory syndrome (IRIS). IRIS is characterized by an excessive and pathologic inflammatory response to antigens derived from opportunistic infections (OIs)<sup>[2]</sup>.

IRIS may manifest in two distinct clinical forms in individuals with HIV infection. Paradoxical IRIS refers to the clinical deterioration of an OI that initially responded to treatment before ART initiation. In contrast, unmasking IRIS occurs when a previously undiagnosed or subclinical OI becomes clinically apparent after ART initiation, resulting in an exaggerated inflammatory response<sup>[3]</sup>. The development of IRIS is influenced by the degree of immune restoration following ART, the underlying antigenic burden, and the genetic susceptibility of the host<sup>[4]</sup>.

IRIS can be triggered by various infectious agents, such as *Mycobacterium tuberculosis*, *Mycobacterium avium* complex

(MAC), herpesviruses, hepatitis B (HBV) and C (HCV) viruses, polyomaviruses, cytomegalovirus (CMV), *Cryptococcus neoformans*, *Pneumocystis jirovecii*, *Toxoplasma gondii*, *Leishmania* spp., and *Strongyloides stercoralis*. In addition, to infectious causes, non-infectious conditions such as autoimmune diseases and malignancies may also contribute to the development of IRIS<sup>[5-7]</sup>.

In our country, the occurrence of IRIS among individuals with HIV infection is considered relatively rare<sup>[8,9]</sup>. This multicenter study was conducted to characterize patients who developed IRIS and to present nationwide data. The aim of this study was to identify both infectious and non-infectious causes of IRIS in patients with HIV infection and to evaluate the clinical characteristics, treatment strategies, and outcomes of these patients.

## Materials and methods

### Study Design

This study was conducted by the Scientific Research Committees of The Association for Prevention of Infectious Diseases (BUHASDER). This retrospective study included patients with HIV infection aged 18 years and older who developed IRIS and were followed between January 2010 and December 2024 across 13 centers in Türkiye.

Medical data were collected from hospital records. A total of 31 patients were identified as having developed IRIS during this period.

The approval was granted by the Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital in accordance with the principles of the Declaration of Helsinki (approval number: 2025/44, date: 12.02.2025). As this was a retrospective study, the requirement for informed consent from participants was waived by the Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital.

### Inclusion Criteria

To ensure diagnostic standardization across participating centers, all centers were provided with a standardized case report form together with the predefined IRIS diagnostic criteria before data collection. Participating investigators were instructed to include only patients who fulfilled these criteria. After data submission, all case report forms were centrally reviewed to verify compliance with the predefined diagnostic criteria. Only patients meeting all diagnostic criteria were included in the final analysis.

Patients were included in the study if they met the following criteria<sup>[10-12]</sup>:

- Onset of clinical symptoms within the first 6 months of ART
- A reduction of  $>1 \log_{10}$  in plasma HIV RNA level

- Presence of an exaggerated and/or atypical inflammatory response
- An increase in CD4+ T-lymphocyte count
- Exclusion of alternative causes of clinical deterioration

### Definitions

**Paradoxical IRIS:** Clinical worsening of a previously diagnosed OI following initiation of ART, despite an initial favorable response to treatment<sup>[3,12]</sup>.

**Unmasking IRIS:** Clinical presentation of a previously undiagnosed OI after ART initiation, accompanied by an exaggerated inflammatory response<sup>[3,12]</sup>.

### Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Because of the small number of deaths, continuous variables were compared between survivors and non-survivors using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher exact test when the expected cell count was less than 5. Continuous variables are presented as median (25<sup>th</sup>-75<sup>th</sup> percentile), whereas categorical variables are expressed as number and percentage (%). A 2-sided p value  $<0.05$  was considered statistically significant.

## Results

During the study period, 970 patients with HIV infection were followed, and 31 (3.2%) developed IRIS. Among these, 87.1% were male, and the median age at ART initiation was 43 years [interquartile range (IQR), 34-50] (Table 1). The mean body mass index was  $21.4 \pm 3.0$ . Laboratory parameters at ART initiation are shown in Table 2.

Integrase inhibitors were administered to 29 (93.5%) patients. In one case, darunavir/ritonavir was switched to dolutegravir because of a drug–drug interaction following TB diagnosis (Table 3). Corticosteroid dose and treatment duration data were available for 19 of the 21 patients who received corticosteroids. The mean corticosteroid dose was  $176.84 \pm 291.91$  mg (median, 80 mg; range, 20-1,000 mg), and the mean treatment duration was  $24.73 \pm 22.44$  days (median, 20 days; range, 1-90 days). In patients with paradoxical IRIS, the mean corticosteroid dose was  $207.14 \pm 337.28$  mg (median, 80 mg; range, 20-1,000 mg), with a mean treatment duration of  $22.57 \pm 22.66$  days (median, 19 days; range, 1-90 days).

In patients with unmasking IRIS, the mean corticosteroid dose was  $92.00 \pm 38.98$  mg (median, 80 mg; range, 60-160 mg), and the mean treatment duration was  $30.80 \pm 23.14$  days (median, 21 days; range, 10-66 days).

**Table 1.** Characteristics of patients with IRIS.

| Characteristics                                | Total<br>(n = 31),<br>n (%) | Paradoxical<br>(n = 21),<br>n (%) | Unmasking<br>(n = 10),<br>n (%) |
|------------------------------------------------|-----------------------------|-----------------------------------|---------------------------------|
| Sex (male)                                     | 27 (87.1)                   | 18 (85.7)                         | 9 (90)                          |
| Sex (female)                                   | 4 (12.9)                    | 3 (14.2)                          | 1 (10)                          |
| <b>Mode of HIV transmission</b>                |                             |                                   |                                 |
| Heterosexual                                   | 11 (35.5)                   | 7 (33.3)                          | 4 (40)                          |
| Male-to-male sexual contact*                   | 11 (35.5)                   | 7 (33.3)                          | 4 (40)                          |
| Bisexual*                                      | 6 (19.3)                    | 4 (19)                            | 2 (20)                          |
| Unknown                                        | 3 (9.7)                     | 3 (14.2)                          | -                               |
| <b>Substance use</b>                           |                             |                                   |                                 |
| Cigarettes                                     | 23 (74.1)                   | 16 (76.1)                         | 7 (70)                          |
| Alcohol                                        | 11 (35.5)                   | 6 (28.6)                          | 5 (50)                          |
| Recreational drugs                             | 7 (22.5)                    | 4 (19)                            | 3 (30)                          |
| <b>Comorbidities</b>                           |                             |                                   |                                 |
| No comorbidity                                 | 27 (87.1)                   | 19 (90.4)                         | 8 (80)                          |
| Chronic hepatitis B                            | 2 (6.4)                     | 1 (4.7)                           | 1(10)                           |
| Diabetes mellitus                              | 1 (3.2)                     | 1 (4.7)                           | -                               |
| Hypertension                                   | 1 (3.2)                     | -                                 | 1 (10)                          |
| <b>Symptoms and signs at the start of IRIS</b> |                             |                                   |                                 |
| Fever                                          | 22 (70.9)                   | 13 (61.9)                         | 9 (90)                          |
| Cough                                          | 13 (41.9)                   | 9 (42.8)                          | 4 (40)                          |
| Sweating                                       | 10 (32.2)                   | 6 (28.5)                          | 4 (40)                          |
| Headache                                       | 9 (29)                      | 7 (33.3)                          | 2(20)                           |
| Shortness of breath                            | 9 (29)                      | 7 (33.3)                          | 2(20)                           |
| Increase in lymph nodes                        | 7 (22.5)                    | 5 (23.8)                          | 2 (20)                          |
| Meningismus                                    | 4 (12.9)                    | 2 (9.5)                           | 2 (20)                          |
| <b>Laboratory results at the start of IRIS</b> |                             |                                   |                                 |
| Increased liver tests                          | 3 (9.6)                     | 1 (4.7)                           | 2 (20)                          |
| Worsening of CSF findings                      | 3 (9.6)                     | 2 (9.5)                           | 1 (10)                          |
| Progression on radiological imaging            | 13 (41.9)                   | 10 (47.6)                         | 3 (30)                          |

\*Self-reported sexual behavior. CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome.

**Table 2.** Laboratory values at the start of antiretroviral therapy.

| Laboratory tests                          | Mean $\pm$ SD       | Median (IQR)           |
|-------------------------------------------|---------------------|------------------------|
| Leukocyte count (cells/mm <sup>3</sup> )  | 6271 $\pm$ 2962     | 5790 (3685-7995)       |
| Lymphocyte count (cells/mm <sup>3</sup> ) | 1031 $\pm$ 758.3    | 900 (585-1419)         |
| Hemoglobin (g/dL)                         | 11.1 $\pm$ 2.2      | 11 (9.9-12.6)          |
| Platelet count (cells/mm <sup>3</sup> )   | 219161 $\pm$ 111006 | 186000 (141500-281000) |
| Creatinine (mg/dL)                        | 0.8 $\pm$ 0.2       | 0.8 (0.7-0.9)          |

IQR, interquartile range; SD, standard deviation.

Ten different opportunistic pathogens were identified as causes of IRIS, with *Mycobacterium tuberculosis* and *Pneumocystis jirovecii* being the most common (Table 4).

Multiple pathogens were detected in four patients: CMV and *Pneumocystis jirovecii* in two cases; CMV, *Pneumocystis jirovecii*, and *Candida* spp. in one case; and CMV, *Mycobacterium tuberculosis*, and HBV in another. MAC and progressive multifocal leukoencephalopathy (PML) were detected simultaneously in one case.

Paradoxical IRIS was observed in 21 patients (67.7%). The mean time to IRIS development following ART initiation was 47.9  $\pm$  48.6 days (median, 30 days; IQR, 16-60 days). For paradoxical IRIS, the mean duration was 47.7  $\pm$  49.3 days (median, 30 days; IQR, 10–60 days), and for unmasking IRIS, it was 48.4  $\pm$  49.5 days (median, 31.5 days; IQR, 19-56 days).

The mean CD4+/CD8+ T-cell ratio at ART initiation was 0.1. HIV RNA levels exceeded 100,000 IU/mL in 23 patients (74.1%). CD4+ T-cell counts at ART initiation were <100 cells/mm<sup>3</sup> in 22 patients (71%) and 100-300 cells/mm<sup>3</sup> in seven patients (22.5%). One patient with a CD4+ T-cell count >300 cells/mm<sup>3</sup> had coinfection with CMV, TB, and HBV. Another patient with a CD4+ T-cell count of 507 cells/mm<sup>3</sup> was being followed for lymphoma. The mean time to HIV RNA negativity in 19 patients was 177.7  $\pm$  115.9 days (median, 170 days; IQR, 77-250 days). CD4+ T-cell counts, HIV RNA levels, and C-reactive protein values at ART initiation and IRIS diagnosis are presented in Table 5. Figure 1 shows the mean CD4+ T-cell counts at ART initiation according to the condition causing IRIS, whereas Figure 2 shows the median HIV RNA levels at ART initiation according to the condition causing IRIS.

Corticosteroids were used in 21 (67.7%) patients, and non-steroidal anti-inflammatory drugs were used in eight patients (25.8%). One patient with IRIS-associated Kaposi sarcoma received doxorubicin. ART was continued in all patients.

Five of the 31 patients with IRIS died during follow-up, resulting in an all-cause mortality rate of 16.1%, and one additional patient developed permanent sequelae. The underlying IRIS-associated conditions among patients who died were PML-associated IRIS (n=2), concurrent PML- and MAC-associated IRIS (n=1), *Cryptococcus neoformans*-associated IRIS (n=1), and lymphoma-associated IRIS (n=1). The characteristics of cases with a fatal outcome are shown in Table 6.

An exploratory mortality analysis was performed by comparing survivors (n=26) and non-survivors (n=5). Non-survivors had significantly higher baseline lymphocyte counts at ART initiation (median, 1,640 vs. 870 cells/mm<sup>3</sup>; p=0.036). CNS involvement (100% vs. 23.1%; p=0.001), PML (p=0.012), lymphoma (p=0.020), meningismus (p=0.048), worsening cerebrospinal fluid findings (p=0.012), and male-to-male sexual contact (p=0.023) were more frequently observed

among non-survivors. No significant differences were observed in age, sex, CD4+ T-cell count, HIV RNA level, corticosteroid

treatment, timing of ART initiation, or time to IRIS development between the 2 groups (Tables 7-11).

**Table 3.** ART used in patients with IRIS.

| ART                            | Total (n = 31), n (%) | Paradoxical (n = 21), n (%) | Unmasking (n = 10), n (%) |
|--------------------------------|-----------------------|-----------------------------|---------------------------|
| TDF/FTC + DTG                  | 14 (45)               | 11 (52)                     | 3 (30)                    |
| TAF/FTC + BIC                  | 9 (29)                | 4 (19)                      | 5 (50)                    |
| TDF/FTC + RAL                  | 2 (6)                 | 2 (9.5)                     | —                         |
| 3TC + DTG                      | 2 (6)                 | —                           | 2 (20)                    |
| TDF/FTC + PI/r                 | 2 (6)                 | 2 (9.5)                     | —                         |
| EVG/COBI/FTC/TDF               | 1 (3)                 | 1 (4.7)                     | —                         |
| TDF/FTC + DTG/PI/r             | 1 (3)                 | 1 (4.7)                     | —                         |
| Corticosteroid dose (mg)*      | 176.84 ± 291.91       | 207.14 ± 337.28             | 92 ± 38.98                |
| Corticosteroid duration (days) | 24.73 ± 22.44         | 22.57 ± 22.66               | 30.8 ± 23.14              |

\*Corticosteroid doses are presented as the initial daily dose, expressed as methylprednisolone equivalents. 3TC, lamivudine; ART, antiretroviral therapy; BIC, bictegravir; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; IRIS, immune reconstitution inflammatory syndrome; PI/r, darunavir/ritonavir; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

**Table 4.** Conditions associated with IRIS development.

| Condition                                 | Total (n = 31), n (%) | Paradoxical (n = 21), n (%) | Unmasking (n = 10), n (%) | CD4+ T-cell count <100 cells/mm <sup>3</sup> , n (%) | HIV RNA level >100,000 IU/mL, n (%) |
|-------------------------------------------|-----------------------|-----------------------------|---------------------------|------------------------------------------------------|-------------------------------------|
| Opportunistic infections                  |                       |                             |                           |                                                      |                                     |
| <i>Mycobacterium tuberculosis</i> (n = 7) | 7 (22.5)              | 6 (28.5)                    | 1 (10)                    | 5 (71.4)                                             | 6 (85.7)                            |
| Hematopoietic                             | 4 (12.9)              | 4 (19)                      | -                         | 3 (42.8)                                             | 3 (42.8)                            |
| Lymphatic                                 | 2 (6.4)               | 1 (4.7)                     | 1 (10)                    | 2 (28.5)                                             | 2 (28.5)                            |
| Pulmonary                                 | 2 (6.4)               | 2 (9.5)                     | -                         | 2 (28.5)                                             | 2 (28.5)                            |
| Gastrointestinal                          | 1 (3.2)               | 1 (4.7)                     | -                         | -                                                    | 1 (14.2)                            |
| <i>Pneumocystis jirovecii</i> (n = 7)     | 7 (22.5)              | 5 (23.8)                    | 2 (20)                    | 7 (100)                                              | 6 (85.7)                            |
| CMV (n = 6)*                              | 6 (19.3)              | 4 (19)                      | 2 (20)                    | 4 (66.6)                                             | 4 (83.3)                            |
| Pulmonary                                 | 6 (19.3)              | 4 (19)                      | 2 (20)                    | 4 (66.6)                                             | 5 (83.3)                            |
| Gastrointestinal                          | 1 (3.2)               | 1 (4.7)                     | -                         | 0 (0)                                                | 1 (16.6)                            |
| Hematopoietic                             | 1 (3.2)               | 1 (4.7)                     | 1 (10)                    | 1 (16.6)                                             | 1 (16.6)                            |
| PML (n = 6)                               | 6 (19.3)              | 6 (28.5)                    | -                         | 5 (83.3)                                             | 2 (33.3)                            |
| <i>Cryptococcus neoformans</i> (n = 3)    | 3 (9.6)               | 1 (4.7)                     | 2 (20)                    | 1 (66.6)                                             | 1 (66.6)                            |
| MAC (n = 2)                               | 2 (6.4)               | 1 (4.7)                     | 1 (10)                    | 2 (100)                                              | 2 (100)                             |
| Toxoplasmosis (n = 2)                     | 2 (6.4)               | 1 (4.7)                     | 1 (10)                    | 2 (100)                                              | 0 (0)                               |
| Hepatitis B (n = 1)                       | 1 (3.2)               | 1 (4.7)                     | -                         | 0 (0)                                                | 1 (100)                             |
| <i>Candida</i> (n = 1)                    | 1 (3.2)               | 1 (4.7)                     | -                         | 1 (100)                                              | 1 (100)                             |
| Kaposi sarcoma (n = 2)                    | 2 (6.4)               | 1 (4.7)                     | 1 (10)                    | 0 (0)                                                | 2 (100)                             |
| Malignancy                                |                       |                             |                           |                                                      |                                     |
| Lymphoma (n = 1)                          | 1 (3.2)               | -                           | 1 (10)                    | 0 (0)                                                | 0 (0)                               |
| IRIS start time (days)                    | 5 (16.1)<br>26 (83.8) | 4 (19)<br>17 (80.9)         | 1 (10)<br>9 (90)          | 3 (60)<br>19 (73)                                    | 3 (60)<br>20 (73)                   |
| >90 days (n = 5)                          | 5 (16.1)              | 3 (14.2)                    | 2 (20)                    | 3 (60)                                               | 2 (40)                              |

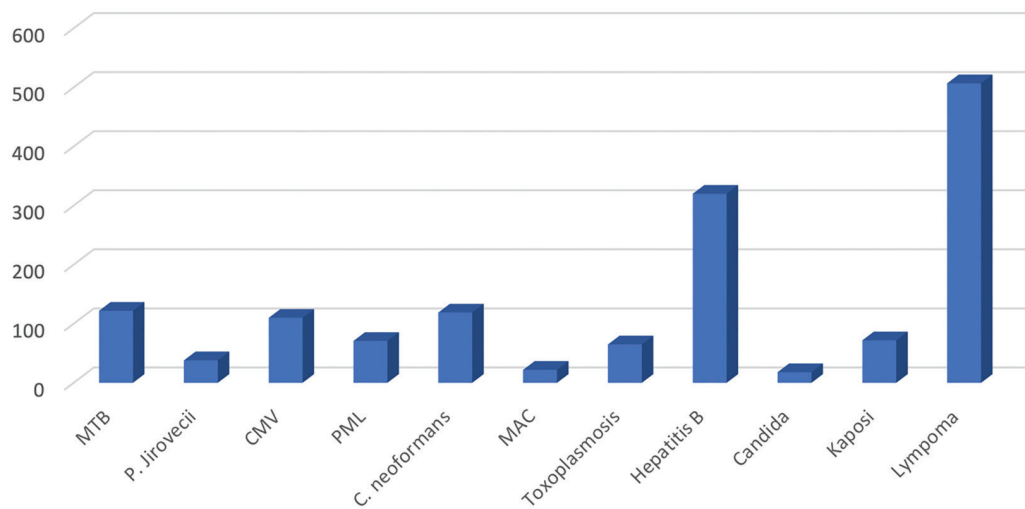
\*CMV infection was detected in a total of 6 patients. In 1 patient, both gastrointestinal and pulmonary CMV infection were present; in another, both the hematopoietic and pulmonary systems were affected. In 4 patients, only the pulmonary system was affected by CMV.

CMV, cytomegalovirus; IRIS, immune reconstitution inflammatory syndrome; MAC, *Mycobacterium avium* complex; PML, progressive multifocal leukoencephalopathy. HIV, human immunodeficiency virus; RNA, ribonucleic acid; IU, international unit.

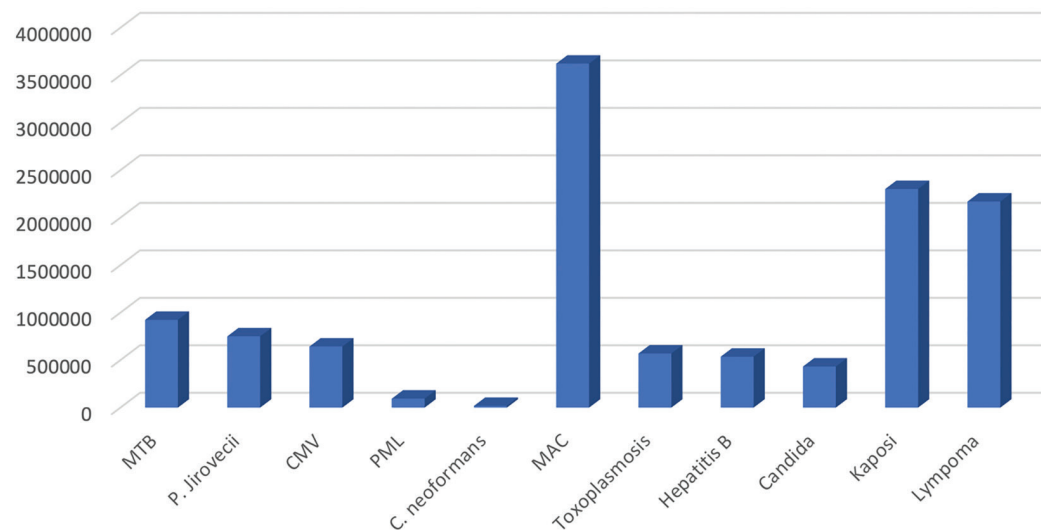
**Table 5.** Laboratory results of patients who developed IRIS.

| Laboratory tests                           | Pre-ART            |                        | Onset of IRIS       |                   |
|--------------------------------------------|--------------------|------------------------|---------------------|-------------------|
|                                            | Mean ± SD          | Median (IQR)           | Mean ± SD           | Median (IQR)      |
| CD4+ T-cell count (cells/mm <sup>3</sup> ) | 101.2 ± 108.6      | 61 (33-117)            | 198.9 ± 222.1       | 125 (78.5-230)    |
| CD4+ T-cell count (%)                      | 8.2 ± 5.2          | 7 (4.7-11.5)           | 15.4 ± 9.1          | 13.1 (8.2-20)     |
| HIV RNA level                              | 3305789 ± 11720715 | 480000 (98250-1371653) | 127901.1 ± 490506.8 | 626.5 (296-2306)  |
| C-reactive protein (mg/dL)                 | 33.3 ± 39          | 15.6 (7.5-39)          | 64.5 ± 75.8         | 31.5 (11.5-105.5) |

IQR, interquartile range; IRIS, immune reconstitution inflammatory syndrome; SD, standard deviation; ART, antiretroviral therapy; HIV, human immunodeficiency virus; RNA, ribonucleic acid.



**Figure 1.** Mean CD4+ T-cell counts at the start of ART. MTB, *Mycobacterium tuberculosis*; CMV, cytomegalovirus; MAC, *Mycobacterium avium* complex; PML, progressive multifocal leukoencephalopathy; ART, antiretroviral therapy.



**Figure 2.** Median HIV RNA levels at the start of ART. MTB, *Mycobacterium tuberculosis*; CMV, cytomegalovirus; MAC, *Mycobacterium avium* complex; PML, progressive multifocal leukoencephalopathy; ART, antiretroviral therapy.

**Table 6.** Characteristics of patients with fatal outcomes.

| Etiologic agent                                    | Site(s) of involvement                                             | Survival after IRIS onset (days) | Treatment                               | Clinical course                                                                             |
|----------------------------------------------------|--------------------------------------------------------------------|----------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------|
| <i>Cryptococcus neoformans</i>                     | Central nervous system, pulmonary system, dermatologic involvement | 4                                | ART                                     | Cardiopulmonary arrest                                                                      |
| Progressive multifocal leukoencephalopathy         | Central nervous system                                             | 82                               | ART, corticosteroid (100 mg for 5 days) | Clinical deterioration with progression of MRI findings                                     |
| Progressive multifocal leukoencephalopathy         | CNS                                                                | 59                               | ART, corticosteroid (80 mg for 45 days) | Comatose state, decerebrate posturing, loss of brainstem reflexes, bilateral Babinski signs |
| MAC and progressive multifocal leukoencephalopathy | CNS, lymphatic system                                              | 7                                | ART                                     | Numbness in the hands and feet, inability to walk, decreased Glasgow Coma Scale score       |
| Lymphoma                                           | CNS, lymphatic system, hematopoietic system                        | 90                               | Chemotherapy                            | Thrombocytopenia and SAH                                                                    |

ART, antiretroviral therapy; CNS, central nervous system; IRIS, immune reconstitution inflammatory syndrome; MAC, *Mycobacterium avium* complex; MRI, magnetic resonance imaging; SAH, subarachnoid hemorrhage.

**Table 7.** Comparison of baseline characteristics between survivors and non-survivors among patients with immune reconstitution inflammatory syndrome.

| Variable                           | Total (n = 31)  | Non-survivors (n = 5) | Survivors (n = 26) | p value |
|------------------------------------|-----------------|-----------------------|--------------------|---------|
| Age, median (IQR), y               | 43 (34-50)      | 44 (40-57)            | 43 (33.25-49.25)   | 0.361   |
| Male sex, n (%)                    | 27 (87.1)       | 5 (100)               | 22 (84.6)          | 0.347   |
| Heterosexual transmission, n (%)   | 11 (35.5)       | 0 (0)                 | 11 (42.3)          | 0.07    |
| Male-to-male sexual contact, n (%) | 11 (35.5)       | 4 (80)                | 7 (26.9)           | 0.023   |
| Bisexual transmission, n (%)       | 6 (19.4)        | 1 (20)                | 5 (19.2)           | 0.968   |
| Smoking, n (%)                     | 23 (74.2)       | 5 (100)               | 18 (69.2)          | 0.15    |
| Alcohol use, n (%)                 | 12 (38.7)       | 3 (60)                | 9 (34.6)           | 0.286   |
| Recreational drug use, n (%)       | 7 (22.6)        | 2 (40)                | 5 (19.2)           | 0.309   |
| Body mass index, kg/m <sup>2</sup> | 21.5 (20–23.25) | 23 (20.0–24.7)        | 21.4 (19.0–23.5)   | 0.521   |
| Presence of comorbidity, n (%)     | 4 (12.9)        | 2 (40)                | 2 (7.7)            | 0.112   |

IQR, interquartile range.

**Table 8.** Laboratory parameters at ART initiation according to mortality among patients with immune reconstitution inflammatory syndrome.

| Variable                                                   | Total (n = 31)         | Non-survivors (n = 5)    | Survivors (n = 26)         | p value |
|------------------------------------------------------------|------------------------|--------------------------|----------------------------|---------|
| WBC count at ART initiation, cells/mm <sup>3</sup>         | 5790 (3650-8090)       | 6310 (5030-9285)         | 5645 (3470-8290)           | 0.420   |
| Lymphocyte count at ART initiation, cells/mm <sup>3</sup>  | 900 (550-1439)         | 1640 (880-3095)          | 870 (487.5-1347.5)         | 0.036   |
| Hemoglobin at ART initiation, g/dL                         | 11 (9.8-12.7)          | 12 (10.4-15.35)          | 10.9 (9.55-12.55)          | 0.188   |
| Platelet count at ART initiation, cells/mm <sup>3</sup>    | 186000 (140000-287000) | 165000 (125500-260500)   | 196000 (137000-290750)     | 0.629   |
| Serum creatinine at ART initiation, mg/dL                  | 0.8 (0.7-0.9)          | 1.0 (0.68-1.325)         | 0.795 (0.70-0.90)          | 0.090   |
| CD4+ T-cell count at ART initiation, cells/mm <sup>3</sup> | 61 (29-126)            | 126 (31-319)             | 58 (29-100.5)              | 0.390   |
| CD4+ T-cell percentage at ART initiation, %                | 7 (4.5-11.7)           | 6 (4-10.45)              | 7.5 (4.3-11.775)           | 0.628   |
| CD8+ T-cell count at ART initiation, cells/mm <sup>3</sup> | 529 (312-972)          | 1180 (250.5-2096.5)      | 516.5 (343.25-817.5)       | 0.420   |
| CD8+ T-cell percentage at ART initiation, %                | 55 (21-70)             | 52 (23-67)               | 62 (53-76)                 | 0.514   |
| HIV RNA level at ART initiation, IU/mL                     | 480000 (94500-1543305) | 450000 (78357.5-3095000) | 508500 (100125-1285826.25) | 0.957   |

ART, antiretroviral therapy; HIV, human immunodeficiency virus; RNA, ribonucleic acid; WBC, white blood cell.

**Table 9.** Comparison of immune reconstitution inflammatory syndrome-associated conditions between survivors and non-survivors.

| Underlying condition associated with IRIS                 | Total (n = 31) | Non-survivors (n = 5) | Survivors (n = 26) | p value |
|-----------------------------------------------------------|----------------|-----------------------|--------------------|---------|
| Toxoplasmosis                                             | 2 (6.5)        | 0 (0)                 | 2 (7.7)            | 0.521   |
| Progressive multifocal leukoencephalopathy                | 6 (19.4)       | 3 (60)                | 3 (11.5)           | 0.012   |
| Pneumocystis jirovecii pneumonia                          | 4 (12.9)       | 0 (0)                 | 4 (15.4)           | 0.347   |
| Tuberculosis                                              | 7 (22.6)       | 0 (0)                 | 7 (26.9)           | 0.187   |
| Disseminated <i>Mycobacterium avium</i> complex infection | 2 (6.5)        | 1 (20)                | 1 (3.8)            | 0.178   |
| Lymphoma                                                  | 1 (3.2)        | 1 (20)                | 0 (0)              | 0.020   |
| Kaposi sarcoma                                            | 2 (6.5)        | 0 (0)                 | 2 (7.7)            | 0.521   |
| Cytomegalovirus diseases                                  | 6 (19.4)       | 0 (0)                 | 6 (23.1)           | 0.232   |
| Cryptococcosis                                            | 3 (9.7)        | 1 (20)                | 2 (7.7)            | 0.394   |

IRIS, immune reconstitution inflammatory syndrome.

**Table 10.** Clinical characteristics and organ involvement according to mortality among patients with immune reconstitution inflammatory syndrome.

| Clinical characteristics                                       | Total (n = 31) | Non-survivors (n = 5) | Survivors (n = 26) | p value |
|----------------------------------------------------------------|----------------|-----------------------|--------------------|---------|
| Central nervous system involvement, n (%)                      | 11 (35.5)      | 5 (100)               | 6 (23.1)           | 0.001   |
| Pulmonary involvement, n (%)                                   | 16 (51.6)      | 2 (40)                | 14 (53.8)          | 0.570   |
| Hematopoietic involvement, n (%)                               | 4 (12.9)       | 1 (20)                | 3 (11.5)           | 0.605   |
| Gastrointestinal involvement, n (%)                            | 3 (9.7)        | 1 (20)                | 2 (7.7)            | 0.436   |
| Dermatologic involvement, n (%)                                | 3 (9.7)        | 1 (20)                | 2 (7.7)            | 0.394   |
| Fever, n (%)                                                   | 22 (71.0)      | 5 (100)               | 17 (65.4)          | 0.118   |
| Cough, n (%)                                                   | 13 (41.9)      | 1 (20)                | 12 (46.2)          | 0.278   |
| Night sweats, n (%)                                            | 10 (32.3)      | 1 (20)                | 9 (34.6)           | 0.522   |
| Headache, n (%)                                                | 9 (29.0)       | 3 (60)                | 6 (23.1)           | 0.096   |
| Dyspnea, n (%)                                                 | 9 (29.0)       | 2 (40)                | 7 (26.9)           | 0.555   |
| Lymphadenopathy, n (%)                                         | 7 (22.6)       | 2 (40)                | 5 (19.2)           | 0.309   |
| Meningismus, n (%)                                             | 4 (12.9)       | 2 (40)                | 2 (7.7)            | 0.048   |
| Elevated liver function tests, n (%)                           | 3 (9.7)        | 0 (0)                 | 3 (11.5)           | 0.424   |
| Worsening cerebrospinal fluid (CSF) findings, n (%)            | 3 (9.7)        | 2 (40)                | 1 (3.8)            | 0.012   |
| Radiological progression, n (%)                                | 13 (41.9)      | 2 (40)                | 11 (42.3)          | 0.924   |
| Paradoxical immune reconstitution inflammatory syndrome, n (%) | 21 (67.7)      | 3 (60)                | 18 (69.2)          | 0.686   |

**Table 11.** Clinical course and treatment according to mortality among patients with immune reconstitution inflammatory syndrome.

| Variable                                              | Total (n = 31) | Non-survivors (n = 5) | Survivors (n = 26) | p value |
|-------------------------------------------------------|----------------|-----------------------|--------------------|---------|
| Time from ART initiation to IRIS onset, days          | 30 (14-60)     | 52 (14-60)            | 29 (13.75-61.25)   | 0.809   |
| Follow-up duration, days                              | 80 (32.5-260)  | 109 (41.5-350)        | 57 (31.25-188.75)  | 0.470   |
| Non-steroidal anti-inflammatory drug treatment, n (%) | 8 (25.8)       | 0 (0)                 | 8 (30.8)           | 0.150   |
| Corticosteroid treatment, n (%)                       | 21 (67.7)      | 2 (40)                | 19 (73.1)          | 0.296   |

ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome.

## Discussion

IRIS has long been recognized as a serious complication in people living with HIV, with reported incidence rates ranging from 3% to 54%, particularly among patients with advanced immunosuppression and a high HIV viral load at ART initiation<sup>[13]</sup>. In our study, IRIS developed in 3.2% of patients, representing the lower end of the reported range. We believe that this relatively low incidence may be explained by several factors. First, our stringent diagnostic criteria, including the systematic reevaluation of all suspected cases according to predefined diagnostic criteria, may have reduced the number of confirmed IRIS cases. Second, the retrospective design may have resulted in underrecognition of mild or undocumented IRIS episodes. Finally, population-specific or genetic factors may also have contributed to the observed incidence<sup>[5,14]</sup>.

A notable finding of our study was that paradoxical IRIS accounted for 68% of all cases, whereas unmasking IRIS was less common. This distribution may be related to the fact that HIV infection was frequently diagnosed during the evaluation of an OI, with the OI typically being identified before the initiation of ART. In contrast, Pérez-Rueda et al.<sup>[13]</sup> reported that 59% of cases were unmasking IRIS, whereas Hoyo-Ulloa et al.<sup>[1]</sup> found unmasking IRIS in 81% of patients. These differences suggest that the relative frequencies of paradoxical and unmasking IRIS may vary according to the timing of HIV diagnosis, the burden of OIs at presentation, and local clinical practice regarding ART initiation.

Both infectious and non-infectious causes may contribute to IRIS development<sup>[7]</sup>. In our study, the most common OIs associated with IRIS were *Mycobacterium tuberculosis* and *Pneumocystis jirovecii*. Previous studies have identified *Varicella zoster*, *Mycobacterium tuberculosis*, MAC, *Pneumocystis jirovecii*, and *Cryptococcus neoformans* as the most common opportunistic pathogens associated with IRIS<sup>[1]</sup>. Similarly, a meta-analysis of 54 studies published between 1998 and 2009, including 1,699 IRIS cases, reported *Mycobacterium tuberculosis*, herpes infections, cryptococcal meningitis (CM), CMV retinitis, and PML as the most frequently associated infections<sup>[11]</sup>. Despite the success of the National Tuberculosis Control Program in reducing TB incidence in our country from 29.4 per 100,000 in 2005 to 11.4 per 100,000 in 2022<sup>[15]</sup>, tuberculosis (TB) remains a public health concern. Therefore, the predominance of TB-IRIS in our population with HIV infection is unsurprising.

In our study, six of the seven TB-IRIS cases (86%) were classified as paradoxical. Furthermore, CD4+ T-cell counts were below 100 cells/mm<sup>3</sup> in 71.4% of these patients, and 85.7% had HIV RNA levels >100,000 IU/mL. The initiation of ART in

patients with TB poses a substantial risk for IRIS, which may cause serious morbidity or even mortality<sup>[16]</sup>. Paradoxical TB-IRIS has been reported in 18%-57% of patients with HIV infection<sup>[17-19]</sup>. The high proportion of paradoxical TB-IRIS and the immunologic characteristics observed in our study are consistent with previously reported risk factors, including a short interval between starting TB treatment and ART, low baseline CD4+ T-cell counts, high baseline viral load, rapid viral suppression, and disseminated TB<sup>[14]</sup>.

In our study, unmasking IRIS developed later than paradoxical IRIS. This finding is consistent with previous reports indicating that the timing of IRIS onset varies according to the underlying pathogen and type of IRIS. IRIS typically develops within 12 weeks of ART initiation. Ratnam et al.<sup>[20]</sup> reported a median onset of 12 weeks, with 65% of cases occurring within the first 3 months of ART. Similarly, Pérez-Rueda et al.<sup>[13]</sup> observed a longer time to IRIS development in patients with unmasking IRIS and parasite-related infections.

In our study, 71% of patients had baseline CD4+ T-cell counts below 100 cells/mm<sup>3</sup>, supporting the well-established association between advanced immunosuppression and the development of IRIS. It is well-established that initiating ART when CD4+ T-cell counts are below 350 cells/mm<sup>3</sup> increases the risk of IRIS<sup>[13]</sup>. Notably, one patient with a CD4+ T-cell count >300 cells/mm<sup>3</sup> had concurrent *Mycobacterium tuberculosis*, CMV, and HBV infections, while another patient with a CD4+ T-cell count of 507 cells/mm<sup>3</sup> was diagnosed with lymphoma following ART initiation. These findings suggest that although severe CD4+ T-cell depletion is a major risk factor, IRIS may also occur in patients with higher CD4+ T-cell counts when other conditions associated with immune dysregulation are present. This observation is consistent with previous reports indicating that immune reconstitution involves not only quantitative CD4+ T-cell recovery but also functional immune changes that may contribute to IRIS pathogenesis<sup>[14]</sup>.

Integrase strand transfer inhibitor (INSTI)-based ART results in more rapid virologic suppression and immune recovery, leading to the hypothesis that it may precipitate earlier IRIS in susceptible patients. However, current evidence, including a meta-analysis of randomized controlled trials, does not support an overall increase in the risk of IRIS with INSTI-based regimens compared with other ART classes<sup>[21]</sup>. In our cohort, 29 of the 31 patients were receiving an INSTI-based ART regimen at the time of IRIS diagnosis. This finding most likely reflects the widespread adoption of INSTI-based regimens as preferred first-line therapy because of their favorable efficacy, tolerability, safety profile, and current guideline recommendations, rather than an association between INSTI use and the development of IRIS. Given the limited sample size and absence of a comparison group, no conclusions can

be drawn regarding the relationship between INSTI-based ART and the risk of IRIS in our cohort.

Of the 31 patients, 21 received corticosteroids; however, detailed data on corticosteroid dose and treatment duration were available for only 19 patients. Among these patients, the mean corticosteroid dose was  $176.8 \pm 291.9$  mg (median, 80 mg), and the mean treatment duration was  $24.7 \pm 22.4$  days (median, 20 days). Current EACS guidelines recommend continuation of ART and treatment of the underlying OI in most cases of OI-associated IRIS, while reserving corticosteroids for patients with life-threatening or severe inflammatory manifestations rather than for routine use. The guidelines provide disease-specific corticosteroid regimens for TB-IRIS and severe PML-IRIS, whereas evidence supporting corticosteroid use in CM-associated IRIS remains limited. For most other forms of IRIS, no specific recommendations regarding corticosteroid dosing or treatment duration are available<sup>[12]</sup>. Therefore, the wide variability in corticosteroid doses and treatment durations observed in our cohort likely reflects the heterogeneous spectrum of underlying OIs and the individualized management of severe IRIS cases.

The reported all-cause mortality among patients with IRIS is approximately 4.5%, although mortality varies substantially according to the underlying OI, access to treatment, diagnostic criteria, degree of immunosuppression, and geographic setting<sup>[22]</sup>. Central nervous system (CNS) involvement has consistently been associated with poor outcomes, with reported mortality rates of 20.8% for CM-IRIS, 22% for PML-IRIS, and up to 75% for CNS TB-IRIS<sup>[7,23]</sup>. In the present study, the all-cause mortality rate was 16.1% (5/31). The IRIS-associated conditions observed among patients who died included PML-associated IRIS (n=2), concurrent PML- and MAC-associated IRIS (n=1), *Cryptococcus neoformans*-associated IRIS (n=1), and lymphoma-associated IRIS (n=1). Consistent with previous reports, CNS involvement and PML were more frequently observed among non-survivors than among survivors. Non-survivors also more frequently presented with meningismus and worsening cerebrospinal fluid findings, suggesting more severe CNS involvement. However, because only 5 deaths occurred, multivariable analysis was not feasible, and these findings should be interpreted as exploratory associations rather than independent predictors of all-cause mortality.

### Study Limitations

Our study was multicenter; however, the number of IRIS cases was limited, and the retrospective design and small sample size were the main limitations. In addition, several subgroup analyses were based on very small numbers of patients.

Therefore, subgroup-specific percentages and mortality rates should be interpreted with considerable caution and regarded as descriptive rather than conclusive, and no generalized conclusions regarding subgroup-specific outcomes can be drawn. Furthermore, a comparison between patients with and without IRIS could not be performed, precluding the identification of factors associated with IRIS development. Nevertheless, published data on HIV-associated IRIS from Türkiye are scarce, and, to our knowledge, no previous multicenter study has comprehensively evaluated the clinical characteristics and outcomes of patients with IRIS across multiple HIV referral centers in the country. Despite its limitations, our study provides valuable multicenter descriptive data on the clinical spectrum, underlying OIs, and outcomes of HIV-associated IRIS in routine clinical practice. Future prospective multicenter studies including larger cohorts and standardized data collection methods are warranted to better define the epidemiology, clinical characteristics, outcomes, and predictors of IRIS development.

## Conclusion

Recognizing the characteristics of patients who develop IRIS and improving awareness of this condition will enable a more informed clinical approach and ensure timely interventions.

### Ethics

**Ethics Committee Approval:** The approval was granted by the Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital in accordance with the principles of the Declaration of Helsinki (approval number: 2025/44, date: 12.02.2025).

**Informed Consent:** As this was a retrospective study, the requirement for informed consent from participants was waived by the Ethics Committee of University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: E.A., F.Y.K., M.T.D., S.A., M.T., Y.Ç., Concept: E.A., D.Ö.E., E.S.A., A.B., M.T.D., S.A., S.Ş., N.T., T.D.Ç., A.Ş.Ç., S.A.N., Ş.K., Design: D.Ö.E., H.Ö.Ö., A.B., T.Ö.K., Y.Ç., S.Ş., T.D.Ç., A.Ş., A.Ş.Ç., Ş.K., Data Collection or Processing: E.A., H.Ö.Ö., F.Y.K., E.S.A., M.T.D., S.A., T.Ö.K., M.T., Y.Ç., N.T., A.Ş., A.Ş.Ç., S.A.N., Analysis or Interpretation: H.Ö.Ö., E.S.A., T.Ö.K., M.T., N.T., T.D.Ç., A.Ş., Literature Search: E.A., D.Ö.E., H.Ö.Ö., F.Y.K., A.B., Ş.K., Writing: E.A., D.Ö.E., F.Y.K., S.A., S.Ş.

**Conflict of Interest:** Yasemin Çağ, MD, serves as an Associate Editor for Mediterranean Journal of Infection Microbes and

Antimicrobials. She had no involvement in the peer review of this article and had no access to information regarding its peer review. No conflict of interest was declared by the other authors.

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