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Contents

Research Articles

The relationship between sleep posture and subacromial impingement syndrome
Alper Yatağanbaba, Çağatay Deniz, Ahmet Emre Süslü, Özgür Ahmet Atay 1

Internal valve graft technique versus spreader graft/autospreader flap in functional rhinoplasty: A prospective cohort study
Süleyman Yıldızdal, Sinan Kadir Altunal, Uğur Koçer 11

Structural changes of pelvic/hip entheses and their evolution over time in psoriatic arthritis patients starting bDMARDs
Gizem Ayan, Abdurrahman Sadıç, Levent Kılıç, Umut Kalyoncu 17

Retrospective analysis of quality of life after trans-sacral epiduroscopic laser neural decompression for chronic back pain
İskender Karakulak, Çiğdem Yalçın, Mehmet Alper Salman, Nalan Çelebi, Altan Şahin 25

The investigation of the inflammation hypothesis in children diagnosed with ASD and ADHD using complete blood count variables
Cihan Aslan, Kevser Nalbant, Dilek Ünal, Buket Kılıç 33

Clinical and cytogenetic characteristics of patients with Triple X syndrome: Experience from a tertiary center
Gizem Ürel Demir, Nazlı Büşra Açıkgöz, Gülen Eda Utine, Pelin Özlem Şimşek Kiper 40

Subclinical inflammation, endothelial dysfunction and atrial electrical remodeling in early-onset paroxysmal atrial fibrillation without comorbidities
Ayşegül Ülgen Kunak, Tolga Kunak, Ali Bayraktar, Kudret Aytemir 46

Single-center real-world data on the efficacy, safety, and current availability of pegylated interferon-α in hematologic neoplasms
Adile Begüm Bahçecioğlu, Yahya Büyükaşık 58

Reconstructive strategies following Fournier's gangrene: A retrospective analysis of outcomes
Etkin Boynuyoğun 67

Coercion in psychiatric inpatients with psychotic and mood disorders: Associations with trauma history, clinical characteristics, and short-term outcomes
Simge Ergün, Ezgi İnce Guliyev 73

Case Report

Pulmonary thromboembolism presenting with multiple cavitary infarcts: A diagnostic challenge with overlap to granulomatous vasculitis
Bilge Sezin Akhan 85

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acta medica RESEARCH ARTICLE

The relationship between sleep posture and subacromial impingement syndrome

Alper Yatağanbaba[1], Çağatay Deniz[2], Ahmet Emre Süslü[2], Özgür Ahmet Atay[1]

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Abstract

Objective: Subacromial impingement syndrome is the most common cause of shoulder pain. One of the possible etiological factors of subacromial impingement syndrome is sleep posture. This study, it is aimed to evaluate the relationship between subacromial impingement syndrome and sleep posture.

Materials and Methods: This study received approval from the Institutional Clinical Research Ethics Committee. (No: 2021/04-54). It included 71 patients who underwent polysomnography at the Ear-Nose-Throat Sleep Laboratory between February and June 2021, meeting the study's inclusion and exclusion criteria. Patients were divided into two groups: 34 who met both diagnostic criteria for subacromial impingement syndrome and 37 who did not meet either criterion. The two groups were compared in terms of demographics, sleep postures, and polysomnography results. Additionally, the relationship between lateral decubitus posture and the affected shoulder was examined in the impingement group.

Results: No significant differences were found between the groups in terms of demographic data, except for smoking (p=0.006). The subacromial impingiment syndrome group spent significantly more time in the lateral decubitus posture than the control group (p=0.003), and they also spent significantly more of their sleep time in the lateral decubitusposition on the painful shoulder (p<0.001). Furthermore, the control group had a significantly higher number of posture changes during sleep (p=0.002).

Conclusion: This study objectively demonstrated the relationship between sleep posture and subacromial impingement syndrome using polysomnography. With this feature, it differs from the limited number of studies that have been done on this subject before. With this study, it has been shown that the lateral decubitus posture during sleeping is a risk factor for subacromial impingement syndrome, and the posture changes during sleep may also be a protective factor for subacromial impingement syndrome.

Keywords: subacromial impingement syndrome, sleep posture, shoulder, shoulder pain

Introduction

Shoulder pain is one of the most commonly encountered problems in orthopedic outpatient clinics. Studies have reported that shoulder pain accounts for up to 30% of all orthopedic outpatient visits [1-3]. In the United Kingdom, the lifetime probability of seeking medical attention for shoulder pain has been shown to range between 20% and 50% [4]. Subacromial impingement syndrome (SIS) is the most commonly encountered condition of the shoulder complex and accounts for 44% to 65% of shoulder pain [5].

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This study was derived from the medical residency thesis of Alper Yatağanbaba, titled "Relationship between sleep posture and subacromial impingement syndrome", conducted under the supervision of Professor Özgür Ahmet Atay at Hacettepe University, Faculty of Medicine, in 2021.

There is no consensus in the literature regarding the pathogenesis and risk factors of SIS. The known and widely accepted risk factors for SIS include advanced age, female gender, obesity, tobacco use, cardiovascular diseases, diabetes mellitus (DM), rheumatoid arthritis (RA), participation in sports involving repetitive overhead movements (e.g., throwing sports, swimming, tennis), working in physically demanding occupations (e.g., painting, electrical work), glenohumeral joint instability, scapular dyskinesis, stiffness in upper extremity joints, thoracic hyperkyphosis, spinal cord injury, history of stroke, Parkinson's disease, and psychosocial factors [6-11].

The most emphasized mechanism in the pathophysiology of SIS is overuse. However, patients with SIS do not always have a history of overuse, nor is the disease consistently observed on the dominant side, which is typically more exposed to stress from active and repetitive movements.

Another possible etiological factor that is less represented in the literature is sleeping posture. According to this theory, sleeping in the lateral decubitus (LD) position increases pressure in the shoulder's subacromial (SA) region on the side being slept on. Suppose this position is maintained for an extended period without movement during sleep. In that case, the high pressure in the SA region may lead to degeneration in the surrounding tissues, ultimately resulting in SIS [12,13].

Supporting this theory, some patients presenting to the clinic with shoulder pain report experiencing pain in the shoulder they sleep on, particularly upon waking up in the morning, which tends to subside after a while. Additionally, the increased prevalence of shoulder pain in patients with conditions such as stroke or spinal cord injury, which negatively affect mobility and the ability to change posture during sleep, suggests that prolonged immobility in the same position during sleep may be a risk factor for shoulder pain [14,15].

The number of studies in the literature investigating the relationship between sleeping posture and SIS is limited, and the data on sleeping posture in these studies are subjectively based on patient self-reports [12,16].

This study aimed to objectively evaluate the relationship between sleeping posture, frequency of posture changes during sleep, sleep quality, and their association with shoulder pain and SIS.

Materials and Methods

This study received approval from the Institutional Clinical Research Ethics Committee. (no: 2021/04-54). No financial support was received.

Within the scope of this study, patients who underwent polysomnography (PSG) at the Department of Ear-Nose-Throat (ENT) Sleep Laboratory between February 2021 and June 2021 were subsequently seen at their post-PSG ENT outpatient follow-up visit, during which an orthopaedic assessment was performed. The indication for the sleep study was either the diagnosis of a sleep disorder or the preoperative/postoperative evaluation of patients who had undergone, or were scheduled to undergo, surgery due to a sleep disorder. A total of 71 patients meeting the inclusion and exclusion criteria were included in the study (Table 1).

Table 1. Inclusion and exclusion criteria

Inclusion Criteria
1. Male gender
2. Age between 40 and 70 years
Exclusion Criteria
1. Working in occupations that involve repetitive shoulder movements, exposure to vibration, or heavy lifting, which are factors contributing to the etiology of SIS
2. Participating in professional or recreational sports known to be associated with SIS etiology, such as tennis, swimming, or javelin throwing
3. Receiving prior treatment for the painful shoulder
4. History of trauma affecting the painful shoulder
5. Bilateral shoulder pain
6. Having additional conditions that could affect sleep posture or movements during sleep (e.g., history of stroke, neurological diseases)
7. Having other conditions that could cause shoulder pain (e.g., cervical disc herniation, peripheral neuropathy, intrathoracic pathologies, rheumatological diseases)
8. Meeting only one of the SIS diagnostic criteria (Table 2).

To minimize confounding factors and ensure a homogenous study population, only male patients aged between 40 and 70 years were included, as age and sex are recognized risk factors for SIS and may influence musculoskeletal pain perception [6-8,17,18]. Patients with occupational or recreational exposures such as repetitive overhead activity, vibration, or heavy lifting, as well as those engaged in sports known to predispose to SIS (e.g., tennis, swimming, javelin throwing), were excluded to avoid overrepresentation of overuse-related etiologies [9,10]. Similarly, individuals with previous treatment or trauma to the painful shoulder, bilateral pain, or comorbid conditions that could alter sleep posture and shoulder mechanics (e.g., stroke, neurological disorders, cervical disc herniation, peripheral neuropathy, intrathoracic pathologies, or rheumatological diseases) were excluded to eliminate alternative causes of shoulder pain [11,14,15,19,20]. Finally, patients who met only one diagnostic criterion for SIS were excluded to ensure diagnostic accuracy and avoid misclassification bias.

Of the 71 patients, those meeting both diagnostic criteria for SIS were included in the SIS group (34 patients), while those not meeting either diagnostic criterion were included in the control group (37 patients). Patients meeting only one diagnostic criterion were excluded from the study (Table 2).

All patients included in the study also completed a questionnaire that inquired about demographic data and the characteristics of their shoulder pain.

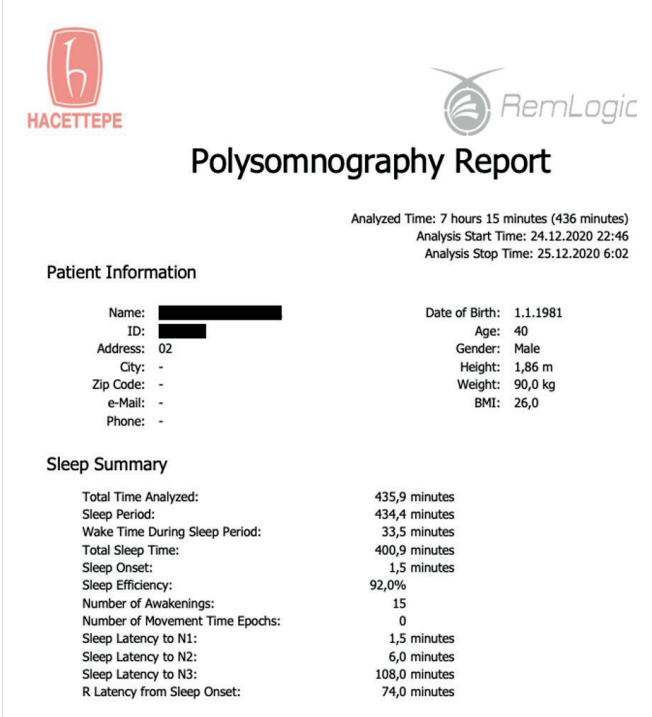
The sleep tests were conducted in the rooms that were soundproofed (<50 decibels), lightproof, maintained at a temperature of 18-20 °C through a ventilation system, and measured between 12-14 m^2 in size. Patients slept on standard medical beds measuring 198 cm in length and 113 cm in width.

Table 2. Diagnostic criteria for SIS

1. Shoulder pain persisting for at least 1 month
2. The positivity of at least 3 out of the 4 clinical diagnostic tests listed below.
a. Painful Arc Test
b. The Neer Impingement Test
c. Hawkins-Kennedy Test
d. Empty Can test

PSG was initiated between 23:00 and 00:00 according to the patients' sleep habits and terminated after a minimum of seven hours of testing. PSG data were recorded using the Embla S450® device. During PSG, the following parameters were recorded: electroencephalography (EEG), electrooculography (EOG), chin electromyography (EMG), leg EMG, airflow, respiratory effort, oxygen saturation, body posture, electrocardiography (ECG), video and audio recordings, and snoring.

Patients' EEG data were recorded using a 6-channel EEG (C4-A1, C3-A2, O2-A1, O1-A2, F4-A1, F3-A2) with probes placed according to the 10-20 system [21]. The data were interpreted by certified specialists trained in PSG. Embla® RemLogicTM software was used for data analysis. EEG waves were evaluated in 30-second epochs. Based on EEG recordings, the durations spent in REM, non-REM, N1, N2, N3, wake time, and sleep onset stages during the sleep period were calculated. Sections with alpha waves in the EEG were classified as wake time, and sections with beta waves were classified as sleep onset. The portions of the recording without alpha or beta waves, indicating the patient was "truly" asleep, were compared to the total sleep period to calculate and record sleep efficiency (Figure 1).


HACETTEPE

RemLogic

Polysomnography Report

Analyzed Time: 7 hours 15 minutes (436 minutes)
Analysis Start Time: 24.12.2020 22:46
Analysis Stop Time: 25.12.2020 6:02

Patient Information

Name:	[redacted]	Date of Birth:	1.1.1981
ID:	[redacted]	Age:	40
Address:	02	Gender:	Male
City:	-	Height:	1,86 m
Zip Code:	-	Weight:	90,0 kg
e-Mail:	-	BMI:	26,0
Phone:	-		

Sleep Summary

Total Time Analyzed:	435,9 minutes
Sleep Period:	434,4 minutes
Wake Time During Sleep Period:	33,5 minutes
Total Sleep Time:	400,9 minutes
Sleep Onset:	1,5 minutes
Sleep Efficiency:	92,0%
Number of Awakenings:	15
Number of Movement Time Epochs:	0
Sleep Latency to N1:	1,5 minutes
Sleep Latency to N2:	6,0 minutes
Sleep Latency to N3:	108,0 minutes
R Latency from Sleep Onset:	74,0 minutes

Figure 1. PSG report sample

The patients' sleep postures were recorded using the Embla S450® position sensor. The recorded data were processed with the Embla® RemLogicTM software to classify body postures during PSG as right LD, left LD, supine, or prone. The proportions of time spent in each posture were calculated relative to the total sleep duration. Additionally, the number of posture changes throughout the test was calculated and recorded.

Finally, the initial follow-up notes from the ENT department after PSG were reviewed to determine whether a treatment was recommended based on the PSG results.

The difference between the patients' self-reported daily sleep duration and their sleep duration recorded during PSG was evaluated for statistical significance. Since the sleep data calculated during PSG using EEG reflect the "actual sleep duration," a more accurate comparison was made by multiplying the patients' self-reported sleep duration by their average sleep efficiency (%) and re-evaluating the difference for statistical significance.

The posture laterality of the patients, specifically the ratios of right and left LD posture to the total LD posture, was calculated.

Posture laterality was calculated using both patient questionnaire data and PSG data. From the questionnaire, the posture laterality (%) of patients who preferred LD sleeping posture and specified a side preference was determined. In the PSG-based evaluation, posture laterality was calculated for both the entire population and the SIS group.

The relationship between the patients' self-reported sleep posture (supine, LD, prone) and their sleep posture during PSG was evaluated. For this, patients whose self-reported sleep posture matched the posture in which they spent the most time during PSG were coded as '1', while those whose self-reported posture differed from their predominant PSG posture were coded as '0'. The proportion of patients coded as '1' relative to the total population was calculated to assess the validity of posture self-reporting through the questionnaire.

The SIS and control groups were compared to evaluate whether there were significant differences in age, BMI, alcohol and tobacco use, and the presence of systemic comorbidities. Additionally, the two groups were compared in terms of the total LD ratio to assess the impact of LD posture on SIS.

In addition, the two groups were compared to evaluate whether there were significant differences in sleep duration during PSG, sleep efficiency, number of posture changes, and the rate of treatment recommendations by the ENT department after PSG. This analysis aimed to investigate potential etiological factors other than the LD posture ratio.

The most critical evaluation within the SIS group was to investigate the relationship between LD posture laterality and the laterality of the painful shoulder. For this calculation, the time spent in right or left LD posture was reclassified for each patient as "time spent on the painful shoulder" and "time spent on the non-painful shoulder", based on the side of the painful shoulder. The significance of the difference between these two values was assessed to determine whether the cause of pain was genuinely related to the increased time spent on the painful shoulder.

Additionally, the laterality of the painful shoulder was calculated by determining the ratio of patients with right shoulder pain and left shoulder pain to the total number of patients in the SIS group. To evaluate whether shoulder pain occurred more frequently on the dominant side, as suggested by the repetitive trauma theory, patients with shoulder pain on their dominant side were compared with those without pain on their dominant side.

In the SIS group, the proportions of the following were calculated relative to the total number of patients in the group: patients whose pain affected their daily life, patients who believed their pain was related to daily activities, patients who thought their pain was associated with their sleeping posture, and patients who experienced shoulder pain upon waking in the morning.

The normality of numerical data used to compare independent groups (SIS group and control group) was assessed with the Shapiro-Wilk test, and the homogeneity of group variances was evaluated using Levene's test. If data were normally distributed at a 95% confidence level and group variances were homogeneous (e.g., height data), parametric tests (Student's t-test) were used. When at least one of these assumptions was not met, non-parametric tests (Mann-Whitney U test) were applied.

For analyzing dependencies between categorical variables, Pearson's chi-square test was used as the assumptions for the test were met. Descriptive statistics for categorical variables were presented as counts and percentages.

For comparisons of numerical measurements within dependent groups (e.g., comparing the time spent on the painful shoulder to the non-painful shoulder in the SIS group), the paired t-test was used as parametric test assumptions were satisfied.

Since no previous studies had evaluated the relationship between time spent in different sleep postures and SIS, a pre-study power analysis could not be conducted. The primary hypothesis of this study was that the proportion of time spent in the LD posture relative to the total sleep duration would differ between the SIS and control groups. A post hoc power analysis of the Mann-Whitney U test used to evaluate this hypothesis indicated a power of 89% at a 95% confidence level for the given sample size (34 patients in the SIS group and 37 in the control group). A p-value of less than 0.05 was considered statistically significant.

Results

A significant difference was found between the patients' self-reported daily sleep duration (mean: 6.6 hours) and the sleep duration recorded via PSG (mean: 5.7 hours) ($p<0.001$). However, this comparison was based on the "actual sleep time" calculated during PSG, excluding periods identified as awake in the EEG recordings. Therefore, the self-reported sleep time was adjusted by multiplying it with the mean sleep efficiency (79.8%) to obtain a calculated value (mean: 5.2 hours). When this adjusted value was compared to the PSG-recorded time (5.7 hours), no significant difference was observed ($p=0.21$).

According to the questionnaire results, 58 patients (81.6%) reported LD, 12 patients (16.9%) reported supine, and only 1 patient (1.4%) reported prone as their preferred sleep posture. Based on PSG results, 56 patients (78.8%) spent the most time in LD posture, while 15 patients (21.2%) spent the most time in supine posture. None of the patients spent the most time in the prone posture during PSG (Table 3 and Table 4).

Among 58 patients who preferred LD sleeping posture on the questionarie, 15 did not indicate a side preference, while 43 specified a side preference. Of those who specified a preference, 24 preferred the right LD posture, and 19 preferred the left LD posture. According to the survey, the lateral preference for posture was calculated as 55.8% right. Based on PSG, the lateral preference for posture across the entire population was found to be 59% right. The survey and PSG results were observed to be consistent.

Among the 43 patients who indicated a side preference for LD posture in the questionnaire, 34 (79%) were found to have consistency between their reported preference and the side they predominantly used during PSG.

Most patients (56 patients, 78.8%) had the same sleep posture in the questionnaire as the posture in which they spent the most time during PSG. The number of patients whose preferred sleep posture matched their PSG sleep posture was significantly higher compared to those whose postures did not match ($p=0.015$).

A significant difference was found between the two patient groups regarding tobacco use ($p=0.006$), while no significant differences were observed for other

Table 3. Comparison of demographic data between patient groups

Demographic data	SIS group	Control Group	p value
Age (years)‡	50 (40-64)	46 (40-67)	0,791
Body mass index (kg/m^2)‡	27,7 (19,8-35,1)	28,4 (22,9-48,4)	0,363
Alcohol consumption (%)	10/34 (%29,4)	11/37 (%29,7)	0,977
Tobacco use (%)	17/34 (%50)	7/37 (%18,9)	0,006
Systemic comorbidity (%)	9/34 (%26,4)	6/37 (%16,2)	0,290
Receiving ENT treatment after PSG (%)	19/34 (%55,8)	19/37 (%51,3)	0,702

‡: Median (minimum-maximum)

Table 4. Comparison of posture and sleep data between patient groups

PSG Data	SIS group	Control Group	P value
PSG total sleep duration (minutes)‡	348,8 (201-422,2)	368,7 (150-420,5)	0,679
Sleep efficiency ((sleep duration / total PSG duration) x 100)‡	80,9 (61,8-95,3)	82,2 (51,4-91,9)	0,982
Total Time Spent in LD Posture (right + left) (%)‡	68,5 (25,3-100)	56,2 (0-86,4)	0,003
Time Spent in Supine Posture (%)‡	25,2 (0-62,8)	41,7 (9,6-100)	<0,001
Number of posture changes in PSG‡	9 (2-20)	14 (7-30)	0,002

‡: Median (minimum-maximum)

demographic variables, including age, BMI, alcohol use, and systemic comorbidities (p>0.05) (Table 3).

Calculations based on PSG data revealed that the SIS group spent significantly more total time in the LD posture compared to the control group (p=0.003). Additionally, the number of posture changes in the SIS group was significantly lower than in the control group (p=0.002) (Table 4).

The average sleep efficiency for the entire population was found to be 79.8%. Additionally, no significant differences were observed between the two groups in terms of sleep time and sleep efficiency (p=0.679 and p=0.982, respectively) (Table 4).

No significant difference was found between the patient groups in terms of the rate of treatment recommendations by the ENT department after PSG (p=0.702).

It was found that the proportion of time SIS patients spent in the LD posture on the painful shoulder (76.9%) was statistically significantly greater than the time spent on the non-painful shoulder (23.1%) (p<0.001).

The laterality of the painful shoulder in the SIS group was calculated as 50%, which was perfectly aligned with the laterality of the sleeping posture, also found to be 50% on the right side. Additionally, no statistically significant relationship was found between the dominant arm and the side of the painful shoulder (p=0.558).

Among the 34 patients in the SIS group, 16 (47%) reported experiencing shoulder pain upon waking in the morning, 19 (55.8%) believed their shoulder pain was related to sleeping posture, 15 (44.1%) thought their shoulder pain was associated with daily activities, and 12 (35.2%) stated that their shoulder pain affected their daily activities.

Discussion

The most implicated theory in the etiology of shoulder pain and SIS is degeneration caused by intrinsic or extrinsic mechanisms due to overuse. The literature suggests that shoulder pain is more common on the right side, as the dominant arm is often the right arm [22-24]. However, for the degeneration mechanism due to overuse to be valid, the individual must subject their active arm to stress, such as repetitive overhead movements. Additionally, studies have shown that pain is not always on the dominant side, regardless of whether there is a history of overuse [19,20].

In this study, the relationship between SIS and sleep posture was investigated. The number of studies addressing the relationship between sleep posture and shoulder pain in the literature is quite limited. In the English literature, the topic was mentioned in a few publications in the 1980s and 1990s [25,26]. In recent years, four studies examining the impact of sleeping posture on shoulder pain have gained prominence [12,13,16,27].

The first recent study on sleeping posture and shoulder pain was published by J. Zenian in 2010. Zenian focused on shoulder pain laterality and concluded that shoulder pain is not always on the same side as the dominant arm. He suggested that pain on the non-dominant side might be due to sleeping posture. Zenian proposed a theory that in the LD posture, increased pressure on the underlying shoulder could lead to degeneration in the structures of the SA region through an extrinsic mechanism [12].

To support his theory, Zenian compared shoulder pain laterality data from eight studies with sleeping posture laterality assessed verbally in two studies and with position sensors in six studies. He found similar results, with shoulder pain laterality at 61.9% right, verbal sleeping posture laterality at 63.2% right, and position sensor data at 61.3% right, suggesting LD posture as a risk factor for shoulder pain [12].

In our study, sleeping posture laterality calculated from the questionnaire (55.8% right) was similar to that calculated from PSG (59% right). Based on this result, the questionnaire appears to be a reliable method for assessing sleeping posture laterality.

In our study, self-reported sleep duration (6.6 hours) was significantly longer than PSG-measured sleep (5.7 hours) ($p<0.001$). Adjusting self-reported data using average sleep efficiency (79.8%) yielded no significant difference from PSG results ($p=0.21$).

The PSG and questionnaire methods were found to yield similar results for sleep posture laterality and sleep duration. Additionally, 78.8% of the population had the same preferred sleep posture (LD, supine, prone) in the questionnaire as the posture they spent the most time in during PSG. This indicates that verbal assessments of sleep posture are highly accurate.

Werner et al. used SA pressure catheters to investigate the effects of different body postures and arm positions on SA pressure in 20 healthy participants. They found that SA pressure was higher in the LD posture and during arm abduction [13]. This finding supported Zenian's theory for the first time [12]. However, since Werner et al.'s [13] study was conducted on healthy individuals, the increased pressure might represent a physiological change without causing pathology. Clinical studies are needed to determine whether this increase, and the LD posture, lead to pathology and pain.

In Kempf et al.'s 2012 study, the sleep posture laterality of 83 patients with shoulder pain was assessed through questionnaires completed by their partners, while shoulder pain laterality was determined through patient surveys. The results showed that a significant majority (67%, $p<0.001$) had shoulder pain on the same side as their LD posture [27].

A similar study by Holdaway et al. [16] in 2018 involved detailed shoulder examinations of 761 workers. Patients with positive Empty Can, painful arc, or Neer impingement tests were classified as having RC tears and grouped accordingly. Using a more detailed questionnaire than Kempf et al.'s [27] study, participants' preferred sleeping postures were identified. This study, however, found no significant relationship between sleeping posture and RC tears.

In Kempf and Holdaway's studies, sleeping posture was assessed solely based on self-reports, and the frequency of posture changes during sleep was not addressed.

The literature shows that shoulder pain is more common in patients with conditions like spinal cord injury, Parkinson's disease, or peripheral neuropathy, where activity levels during sleep and daily life are reduced [28-30]. However, no studies have evaluated the relationship between sleep posture change frequency and shoulder pain in individuals without comorbidities.

This study aimed to address a gap in the literature by objectively evaluating the relationship between sleeping posture preference, posture change frequency during sleep, and SIS using PSG data.

The study found that SIS patients spent significantly more time in the LD posture compared to the control group ($p=0.003$). Additionally, within the SIS group, 76.9% of the total LD posture time was spent on the painful shoulder, compared to 23.7% on the non-painful shoulder, a statistically significant difference ($p<0.001$).

The study found that the posture change frequency was significantly lower in the SIS group compared to the control group ($p=0.002$).

Werner et al. and Holdaway et al. noted in their studies that, in addition to sleeping posture, arm position might also influence shoulder pain. Werner et al. demonstrated that SA pressure increases during arm abduction [13,16]. One limitation of our study is the lack of evaluation of arm position.

Another limitation of the study is that it assessed patients' sleep patterns for only one night in the hospital, which might not fully reflect their habitual sleep behavior. However, this limitation is unlikely to have a significant impact, as sleep efficiency data support its validity. In sleep literature, healthy adults are expected to have an EEG-calculated sleep efficiency of over 80% [31]. Our study showed that, despite being

conducted in a population likely to have sleep problems, the average sleep efficiency was close to normal at 79.8%. Additionally, there was no significant difference in sleep efficiency between the study groups (p = 0.982). These findings suggest that while hospital sleep quality might be lower than at home, this difference is not large enough to affect the study results significantly.

During PSG, the numerous additional probes attached to patients, beyond the posture and EEG probes, may have influenced posture changes and sleep quality. However, the fact that sleep efficiency values remained close to normal suggests that these factors did not significantly impact the results.

In our study, the absence of imaging methods, injections, or diagnostic arthroscopy for confirming diagnoses could be seen as a limitation. However, SIS is primarily a clinical diagnosis [32]. Patients with shoulder pain lasting at least one month and who tested positive in three out of four highly specific and sensitive diagnostic tests (painful arc test, Neer impingement test, Hawkins-Kennedy test, and Empty Can test) were included in the SIS group.

The choice to include only male participants was based on the consideration that menopause or menstrual cycles in women could influence musculoskeletal problems and pain thresholds. This decision was made to eliminate these potential variables [17,18].

Conclusion

The etiology and pathophysiology of SIS remain controversial. Sleep posture has been proposed as a potential factor, but previous studies have been limited and largely based on subjective reports.

This study showed that sleeping in the lateral decubitus posture on the affected shoulder increases the risk of SIS, while frequent posture changes may be protective. It also demonstrated consistency between polysomnography and survey data, confirming the reliability of patient self-reporting for sleep posture.

Based on these findings, it is recommended to ask patients about their sleep posture during history-taking in outpatient clinics. Patients with shoulder pain who prefer sleeping in the LD posture can be advised to adjust their sleeping position. To reduce the time patients spend in the lateral decubitus posture, methods used in the positional treatment of obstructive sleep apnea may be utilized. Different devices such as tennis balls, vests, positional alarms, verbal instruction, and pillows have been used to modify sleep posture in obstructive sleep apnea [33-35].

Author contributions

Conception and design: A.Y.; Data acquisition: A.Y., C.D., A.E.S., O.A.A.; Data analysis: A.Y., O.A.A.; Data interpretation: A.Y., C.D., A.E.S., O.A.A.; Drafting of the manuscript: A.Y., C.D., A.E.S., O.A.A.; Critical revision of the manuscript: A.Y., C.D., A.E.S., O.A.A. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Ethics Boards and Comissions (Date: Febuary 23, 2021, Decision/Protocol No: 2021/04-54). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

Internal valve graft technique versus spreader graft/autospreader flap in functional rhinoplasty: A prospective cohort study

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Abstract

Objective: To compare a novel internal nasal valve graft technique with conventional spreader graft and autospreader flap methods in functional rhinoplasty, with respect to both functional and aesthetic outcomes.

Materials and Methods: Forty patients undergoing primary rhinoplasty were prospectively enrolled and randomly allocated into two groups (n = 20 per group). Group 1 received a conventional spreader graft or autospreader flap, whereas Group 2 underwent the internal nasal valve graft technique, in which cartilage was positioned caudal to the conventional spreader graft line to augment the internal nasal valve without increasing dorsal width.

Results: Preoperative dorsal widths and NOSE scores were comparable between the two groups. At 1-year follow-up, Group 1 demonstrated a statistically significant increase in dorsal width, whereas no significant change was observed in Group 2. NOSE scores improved significantly within both groups, with no statistically significant difference between the groups.

Conclusion: The internal nasal valve graft technique provides functional improvement comparable to that of conventional methods while preventing dorsal widening, thereby representing an effective alternative in functional rhinoplasty that preserves the natural dorsal contour.

Keywords: rhinoplasty, nasal obstruction symptom evaluation, ınternal nasal valve, spreader graft, functional outcomes

Introduction

Rhinoplasty is regarded as one of the most technically demanding facial procedures, as it must simultaneously achieve both aesthetic harmony and functional integrity of the nasal airway [1]. Increasingly, surgical success is evaluated not only by postoperative nasal appearance but also by the preservation or enhancement of nasal breathing, with particular emphasis on the internal nasal valve as a key determinant of airflow. Anatomically situated between the septum and the upper lateral cartilages, the internal nasal valve constitutes the narrowest segment of the nasal airway and accounts for approximately 50% of total nasal airway resistance [2,3]. Even minimal reductions in the valve angle may result in clinically significant airflow compromise, consistent with the principles described by Poiseuille's law [4]. Consequently, preservation or reconstruction of the internal nasal valve is a critical component of contemporary rhinoplasty [5].

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The most frequent iatrogenic cause of internal nasal valve dysfunction is dorsal hump resection. Detachment of the upper lateral cartilages from the septum during this maneuver weakens midvault structural support and predisposes the valve to collapse [1,6]. This may lead not only to functional airway obstruction but also to characteristic aesthetic deformities, such as midvault narrowing and the inverted-V deformity[1]. To mitigate these adverse outcomes, several reconstructive strategies have been developed, most notably the use of spreader grafts.

The spreader graft technique, first described by Sheen in the 1980s, involves placement of cartilage between the septum and upper lateral cartilages to widen the internal nasal valve angle, restore laminar airflow, preserve dorsal aesthetic lines, and provide additional support in cases of septal deviation [1,3]. Multiple studies have demonstrated significant functional improvement following spreader graft placement, as reflected by reductions in NOSE and VAS scores. Furthermore, systematic reviews suggest comparable functional efficacy between traditional spreader grafts and autospreader flap techniques [7].

Despite their widespread use, classic spreader grafts have notable limitations. Lateral displacement of the dorsal aesthetic lines may result in undesirable dorsal widening, a concern that is particularly pronounced in thin-skinned patients [2,8]. Additionally, the need for long, rigid cartilage grafts increase operative complexity, and limited graft availability may constrain their application. Comparative analyses indicate that while butterfly grafts may offer functional outcomes similar to spreader grafts, they often produce more pronounced lateralization and, in some cases, superior functional improvement [8].

Several modifications to the original spreader graft concept have been proposed, including the autospreader flap, bilateral extended spreader grafts (BESG), and composite dorsal augmentation techniques. The autospreader flap obviates the need for additional graft material through folding of the upper lateral cartilages, whereas BESG provides more extensive septal support but may still contribute to dorsal widening [6,9]. Composite techniques—such as diced cartilage wrapped in fascia or gap grafts—are technically more demanding and may be associated with increased morbidity [10]. Importantly, emerging evidence suggests that the level and orientation of graft placement play a decisive role in determining both functional and aesthetic outcomes [2].

Recent meta-analyses show that functional rhinoplasty yields significant improvements in NOSE, VAS, and SNOT-22 scores[5]. Nevertheless, considerable aesthetic variability persists among different surgical techniques [7]. In the present study, we introduce the internal nasal valve graft technique, which involves positioning cartilage caudal to the conventional spreader graft line to selectively expand the internal nasal valve while avoiding dorsal widening. We hypothesize that this technique preserves the functional benefits of traditional spreader grafts while maintaining a more natural dorsal contour.

Materials and Methods

This is a prospective cohort study conducted in a tertiary care plastic surgery department between 2023 and 2025. Ethical approval was obtained from the institutional review board (Decision No. E-93471371-514.10-244516005), and written informed consent was secured from all participants in accordance with the principles of the Declaration of Helsinki.

Patients aged 18 years or older who underwent primary rhinoplasty were eligible for inclusion. Exclusion criteria comprised a history of previous nasal surgery and the need for postoperative nasal interventions, either surgical or medical. A total of 40 patients were enrolled and allocated into two groups of equal size (n = 20 each). Group 1 (control group) underwent reconstruction with a conventional spreader graft or autospreader flap, whereas Group 2 (experimental group) received the internal nasal valve graft technique, in which cartilage was positioned caudal to the conventional spreader graft line to enlarge the internal nasal valve without inducing dorsal widening. Demographic variables, including age and sex, were recorded for all participants.

All procedures were performed using an open rhinoplasty approach. In surgery, all lateral osteotomies were performed in a standardized low-to-low fashion bilaterally by the same senior surgeon in all patients, regardless of study group, to minimize variability that could influence postoperative dorsal width measurements. No excision was performed from the caudal margin of the upper lateral cartilage in either group. Preservation of the caudal border of the upper

lateral cartilage was intentionally maintained to avoid compromising midvault stability and to prevent potential postoperative internal nasal valve insufficiency. After standardized surgery, in group 1, following dorsal hump resection, stabilization of the internal nasal valve region was achieved using a spreader graft or autospreader flap. In group 2, following dorsal hump reduction, a cartilage graft was positioned caudal to the conventional spreader graft plane, along the internal nasal valve region, rather than between the septum and upper lateral cartilages at the dorsal septal level. The graft was placed parallel to the septum and secured to selectively widen the internal nasal valve angle without lateralizing the dorsal aesthetic lines. This graft positioning allows targeted support of the internal nasal valve while preserving dorsal width (Figure 1).

Standardized frontal facial photographs were obtained preoperatively and at 12 months postoperatively under identical lighting conditions, with a fixed camera-to-subject distance of 1.5 m. Interpupillary distance (IPD) was measured in millimeters by an ophthalmologist. Using Fiji (ImageJ) software, the IPD measured in pixels was calibrated to the actual IPD value via the "Set Scale" function. Dorsal width was subsequently assessed by drawing two parallel lines along the nasal dorsum and recording the perpendicular distance between them (Figure 2).

Measurements were made on both preoperative and postoperative photographs. Each measurement was performed twice by the same investigator, and the mean of the two values was used for analysis to minimize interobserver variability.

Nasal function was evaluated using the Nasal Obstruction Symptom Evaluation (NOSE) scale which consists of five items scored on a 0–4 Likert scale[11]. The validated Turkish version of the NOSE questionnaire was administered preoperatively and at 12 months postoperatively[12,13].

Continuous variables were reported as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Between-group comparisons were conducted using the student's t-test for parametric data and the Mann–Whitney U test for nonparametric data. Within-group preoperative and postoperative comparisons were performed using the paired t-test or the Wilcoxon signed-rank test, as appropriate. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

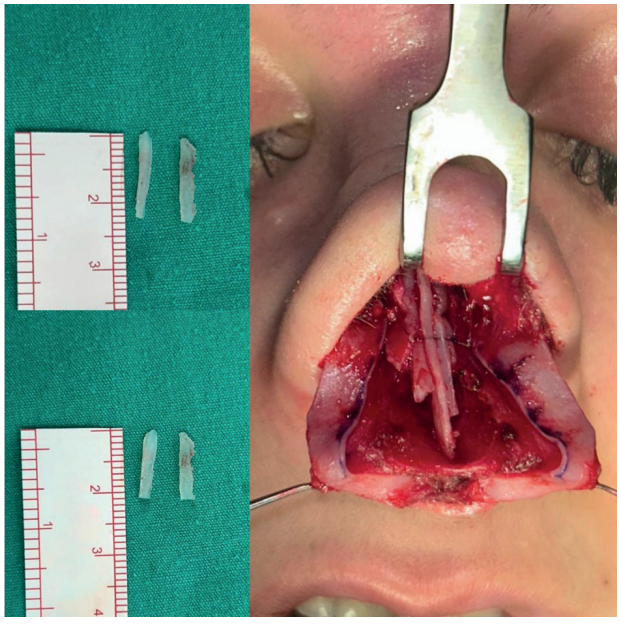

Figure 1. Internal valve graft placement

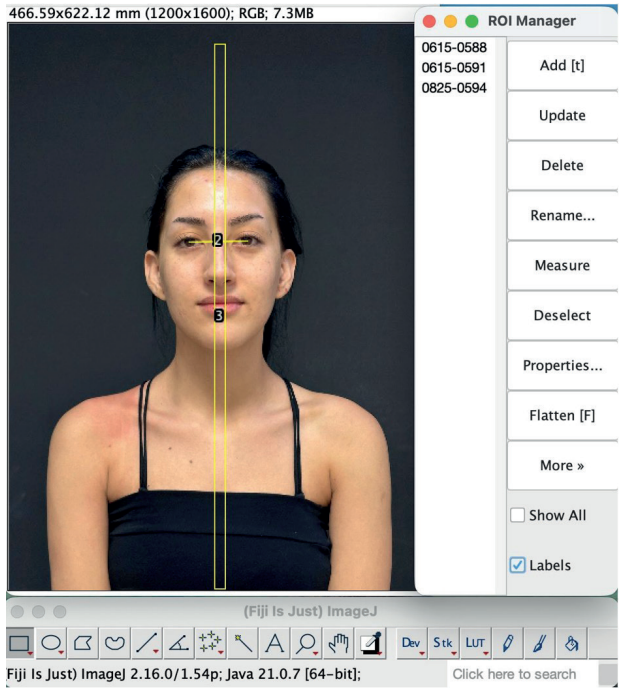

Figure 2. Dorsal width measurement

Results

A total of 40 patients were included in the analysis, with 20 patients in Group 1 and 20 patients in Group 2. The two groups were comparable in terms of age and sex distribution, with no statistically significant differences observed ($p > 0.05$) (Table 1).

Preoperative dorsal width measurements did not differ significantly between the groups ($p > 0.05$). At the 12-month follow-up, Group 1 demonstrated a statistically significant increase in dorsal width compared with baseline ($p < 0.05$), whereas no statistically significant change was observed in Group 2 ($p > 0.05$). Intergroup analysis revealed that postoperative dorsal width was significantly greater in Group 1 than in Group 2 ($p < 0.05$) (Table 2).

Baseline NOSE scores were comparable between the two groups ($p > 0.05$). At 12 months postoperatively, both groups exhibited a significant reduction in NOSE scores, indicating marked improvement in nasal obstruction symptoms ($p < 0.001$ for both). No statistically significant difference was detected between the groups with respect to postoperative NOSE scores ($p > 0.05$) (Table 3).

From a functional standpoint, both surgical approaches resulted in comparable improvements in nasal airway function. Aesthetically, however, dorsal widening was observed in Group 1, whereas Group 2 maintained stable dorsal width, reflecting preservation of the natural dorsal contour. (Figure 3, Figure 4).

Table 1. Demographic characteristics

Variable	Group 1 (n=20)	Group 2 (n=20)	p
Age (years, mean ± SD)	28.5 ± 5.0	27.9 ± 4.4	0.699
Sex (F/M)	11/9	10/10	1.000

Table 2. Preoperative and postoperative dorsal width (mm)

	Preop (Mean ± SD)	Postop (Mean ± SD)	p (within)
Group 1 (Spreader/ Autospreader)	10.98 ± 0.9	12.50 ± 1.0	<0.001
Group 2 (Internal valve graft)	10.88 ± 1.0	11.00 ± 1.1	0.420
p (between)	0.712	<0.001	–

Table 3. Preoperative and postoperative NOSE scores

	Preop (Mean ± SD)	Postop (Mean ± SD)	p (within)
Group 1	15.2 ± 2.1	5.8 ± 2.0	<0.001
Group 2	15.0 ± 2.0	5.5 ± 1.9	<0.001
p (between)	0.730	0.431	–

Discussion

In this prospective study, we compared a novel internal nasal valve graft technique with conventional spreader graft and autospreader flap methods in functional rhinoplasty. The findings demonstrate that the internal valve graft achieves functional outcomes comparable to those of established techniques while effectively avoiding the undesirable dorsal widening commonly associated with classic spreader grafts.

Since its original description by Sheen, the spreader graft has been widely regarded as the standard technique for midvault reconstruction [3]. By increasing the internal nasal valve angle, it restores laminar airflow, preserves continuity of the dorsal aesthetic lines, and provides structural support in the presence of septal deviation [1,7]. Numerous studies have reported significant postoperative improvements in patient-reported outcomes, including reductions in NOSE scores and high levels of patient satisfaction [7]. Similarly, the autospreader flap has gained popularity in primary rhinoplasty due to its technical simplicity and elimination of the need for additional graft harvesting, while offering functional results comparable to those of traditional spreader grafts [6].

Despite these advantages, dorsal widening remains a well-recognized limitation of classic spreader grafts, particularly in thin-skinned patients in whom subtle contour changes are more readily apparent [2,8]. Moreover, the requirement for long, rigid cartilage grafts increases operative complexity and may pose challenges in patients with limited septal cartilage reserves [8]. Alternative strategies, including butterfly grafts, bilateral extended spreader grafts (BESG), and composite augmentation techniques, have been proposed to address these concerns; however, each

Figure 3. Group 1 patient preoperative and postoperative 1st year photographs

Figure 4. Group 2 patient preoperative and postoperative 1st year photographs

carries its own technical demands and potential drawbacks [9,10]. Consistent with previous reports, our findings underscore the importance of graft placement plane and orientation as critical determinants of both functional and aesthetic outcomes [2].

In our experience, the internal nasal valve graft technique provided functional improvement equivalent to that achieved with conventional methods, while preserving the natural dorsal contour. This suggests that positioning the graft caudal to the conventional spreader graft line allows selective expansion of the internal nasal valve without inducing dorsal lateralization. An additional advantage of this technique is the reduced requirement for long cartilage grafts, which may be particularly advantageous in patients with limited graft availability.

Importantly, no excision was performed from the caudal margin of the upper lateral cartilage in this technique. Preservation of this anatomical region is critical for maintaining midvault stability and internal nasal valve competence. Resection of the caudal upper lateral cartilage may predispose patients to postoperative internal valve collapse unless adequately compensated with structural grafting. By avoiding cartilage excision and instead providing targeted caudal support with an internal nasal valve graft, the described technique enhances valve patency while preserving native cartilage anatomy and dorsal aesthetic lines. In cases where caudal upper lateral cartilage resection is unavoidable, we recommend simultaneous reinforcement of the internal nasal valve to prevent secondary functional compromise.

Several limitations of this study should be acknowledged. The sample size was relatively modest (n = 40), and follow-up was limited to one year. Furthermore, functional assessment relied primarily on patient-reported NOSE scores and photographic measurements of dorsal width. Future studies incorporating objective airflow assessments, such as acoustic rhinometry or rhinomanometry, would provide a more comprehensive evaluation of functional outcomes.

In conclusion, the internal nasal valve graft technique appears to be a promising alternative in functional rhinoplasty, offering functional improvements comparable to those achieved with spreader grafts while minimizing dorsal widening. Larger, long-term studies are warranted to further validate the durability and broader applicability of this technique.

Author contributions

Conception and design: S.Y., S.K.A., U.K.; Data acquisition: S.Y., S.K.A., U.K.; Data analysis: S.Y., S.K.A., U.K.; Data interpretation: S.Y., S.K.A., U.K.; Drafting of the manuscript: S.Y., S.K.A., U.K.; Critical revision of the manuscript: S.Y., S.K.A., U.K.. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Ankara Training and Research Hospital Ethics Committee (Date: May 23, 2024, Decision/Protocol No: E-93471371-514.10-244516005). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica

RESEARCH ARTICLE

Structural changes of pelvic/hip entheses and their evolution over time in psoriatic arthritis patients starting bDMARDs

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Abstract

Objective: This study aimed to investigate the frequency and progression of pelvic and hip entheseal structural changes in PsA patients initiating biologic therapy.

Methods: Records from the Hacettepe University Rheumatology Biologic Therapy Registry (HUR-BIO) were retrospectively reviewed. PsA patients with pelvic radiographs obtained within ±1 year of biologic therapy initiation were included. Radiographs were assessed according to the modified New York criteria, and entheseal involvement at the ischium, symphysis pubis, iliac wings and greater/ lesses trochanter was graded from 0 (none) to 4 (florid new bone formation). Grade 2 or higher was considered clinically relevant. Demographic and clincal characteristics were compared between patients with/ without structural changes and progression of these lesions were assessed.

Results: A total of 108 patients (68.5% female; mean age 41.5 ± 11.6 years; mean PsA duration 2.2 years) were included. Baseline mNY positivity was detected in 45.4%. Bilateral relevant entheseal involvement was observed in 21.9% at the ischium, 15.3% at the symphysis pubis, and 7.7% at the iliac wings. Greater trochanteric enthesopathy was 2% on the right side. Male patients, with higher BMI and older age with family history tended to have more structural lesions. After a mean follow-up of 38.6 months, data from 48 patients were available. Most progression was limited to a one-grade increase at the ischium (28%).

Conclusion: Major pelvic entheseal lesions, predominantly at the ischium and symphysis pubis, are relatively common in PsA but show minimal radiographic progression under biologic therapy.

Keywords: xray, psoriatic arthritis, enthesitis, pelvis

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease characterized by a heterogeneous pattern of clinical manifestations affecting multiple that are considered when treating patients, such as peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail involvement [1]. Among these, enthesitis, the inflammation at the tendon or ligament insertion into bone, is considered a hallmark feature of PsA [2]. Although enthesitis is most commonly assessed and reported using ultrasound, evaluation of deeper regions such as the pelvis and hips requires alternative imaging modalities. Magnetic resonance imaging (MRI) is valuable for detecting active entheseal inflammation; however, its use is limited by

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higher costs, longer acquisition times, and logistical constraints [2]. Over the long term, structural changes can also be visualized radiographically, including cortical bone irregularities, erosions, calcifications, and new bone formation, which may serve as indicators of entheseal involvement in the pelvic and hip regions.

Previous studies have suggested that pelvic entheseal involvement, frequently in PsA [3,4]. However, the literature on the prevalence, distribution, and clinical characteristics of patients with structural pelvic entheseal involvement remains limited, and the longitudinal progression of these lesions has not been systematically evaluated.

Therefore, the aim of this study was to assess pelvic entheseal involvement, including the ischium, iliac wings, symphysis pubis, and the greater and lesser trochanters, on conventional radiography, and to examine its progression over time in a cohort of PsA patients treated with biologic DMARDs.

2. Materials and Methods

2.1. Patient Selection

The Hacettepe University Rheumatology Biologic Database (Hacettepe) is a single-center registry established in 2005, which includes patients with inflammatory arthritis receiving biologic DMARDs (bDMARDs). For this study, patients from the HUR-BIO PsA cohort who had at least one anteroposterior (AP) or Ferguson-view pelvic X-ray obtained within ±1 year of bDMARD initiation were included, regardless of the presence or absence of sacroiliitis on imaging (Figure 1). All patients had a clinical diagnosis of psoriatic arthritis (PsA) confirmed by the treating rheumatologist, and it was recorded whether they fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR).

2.2. Patient and Clinical Data Collection

The following data were recorded: sex, age, and age at PsA diagnosis. Additional baseline variables included smoking status, and presence of obesity (BMI >30) at the time of bDMARD initiation. Clinical features such as history of dactylitis (yes/no), enthesitis (based on the Leeds Enthesitis Index), and nail involvement (including pitting, onycholysis, and hyperkeratosis) were noted. Patient-reported outcomes (PROs) and C-reactive protein (CRP) levels were also recorded at the visit when bDMARD therapy was initiated.

2.3. Ethical Approval

The study was approved by the Ethics Committee of the Hacettepe University Faculty of Medicine (Approval No: KA-22005) and conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki. Informed consent was obtained from all participating patients.

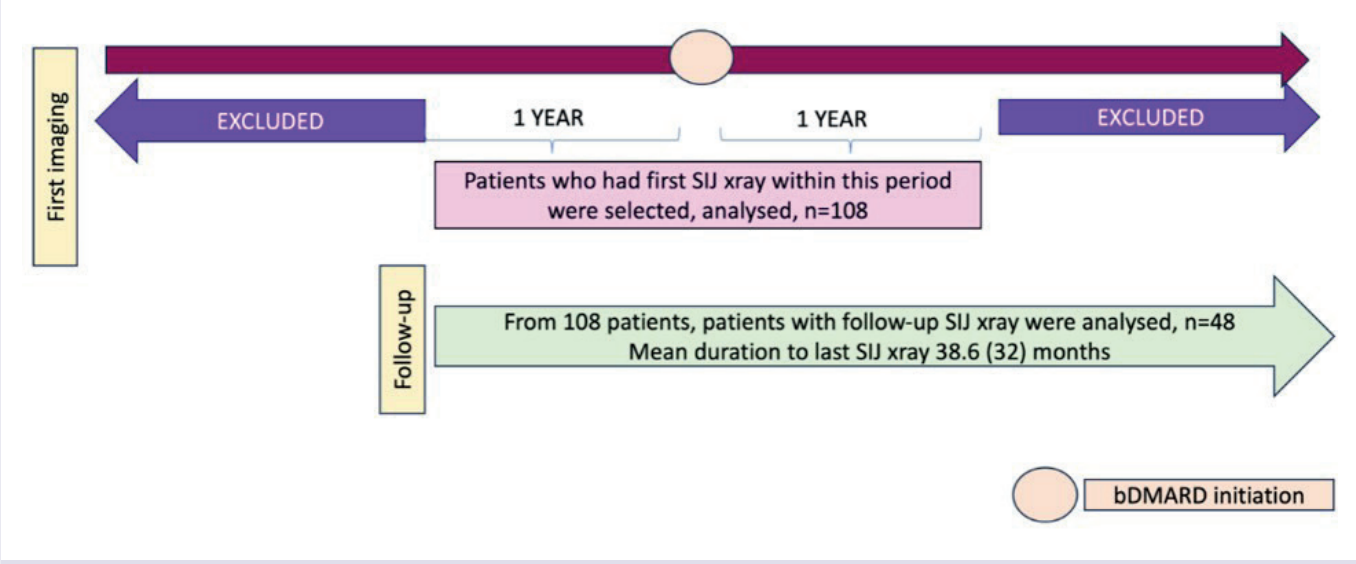

Figure 1. Study timeline

2.4. Pelvic and Lumbar X-ray Assessment and Definitions

Pelvic X-rays were reviewed by an experienced rheumatologist (UK). In cases of suspicion regarding structural findings, the images were jointly re-evaluated by two rheumatologists (UK and LK) until a consensus was reached. Radiographs were assessed according to the modified New York (mNY) criteria (grades 0–4). In addition, entheseal changes were graded at the ischium, symphysis pubis, iliac wings and greater and lesser trochanter as follows: Grade 0: none, Grade 1: minimal, Grade 2: moderate, Grade 3: advanced, and Grade 4: florid new bone formation [4]. Grades 2 and higher were considered to represent clinically relevant changes [4]. When parts of the pelvis were outside the imaging field or obscured by overlying structures, the findings were recorded as "missing." Among the selected patients, those with available follow-up radiographs were evaluated longitudinally using baseline and final images to determine structural progression. Figure 2 provides an example of grading for the ischium

2.5. Statistical Analysis

All analyses were performed using Stata SE v18 (StataCorp, College Station, TX, USA). Data normality was evaluated both visually (histograms, probability plots) and analytically (Kolmogorov–Smirnov test, skewness, and kurtosis). Continuous variables were summarized as mean (standard deviation, SD) or median [interquartile range, IQR], while categorical variables were expressed as frequencies and percentages.

Between-group comparisons for continuous data were conducted using the Student's t-test or Mann–Whitney U test, depending on the distribution. Paired t-tests or Wilcoxon signed-rank tests were used for within-group comparisons. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Results for count data were reported as valid percentages.

3. Results

3.1. Patient characteristics, differences according to the pelvic entheseal involvement severity

A total of 108 patients were included in the study, of whom 74 (68.5%) were female. The mean (SD) age at the time of the first pelvic radiograph was 41.5 (11.6) years, and the mean PsA disease duration was 2.2 years. CASPAR criteria positivity was observed in 66 (61.1%) of patients. A history of enthesitis at any time was reported in 23 (43.4%). Based on baseline pelvic radiographs, 49 (45.4%) of patients were positive according to the modified New York (mNY) criteria.

Regarding clinically relevant pelvic enthesopathies, bilateral involvement was detected in 16 (21.9%) patients at the ischium, 13 (15.3%) patients at the symphysis pubis, and 6 (7.7%) patients at the iliac wings. Clinically relevant major trochanter enthesopathy was observed in 2 (2.2%) patients on the right. On

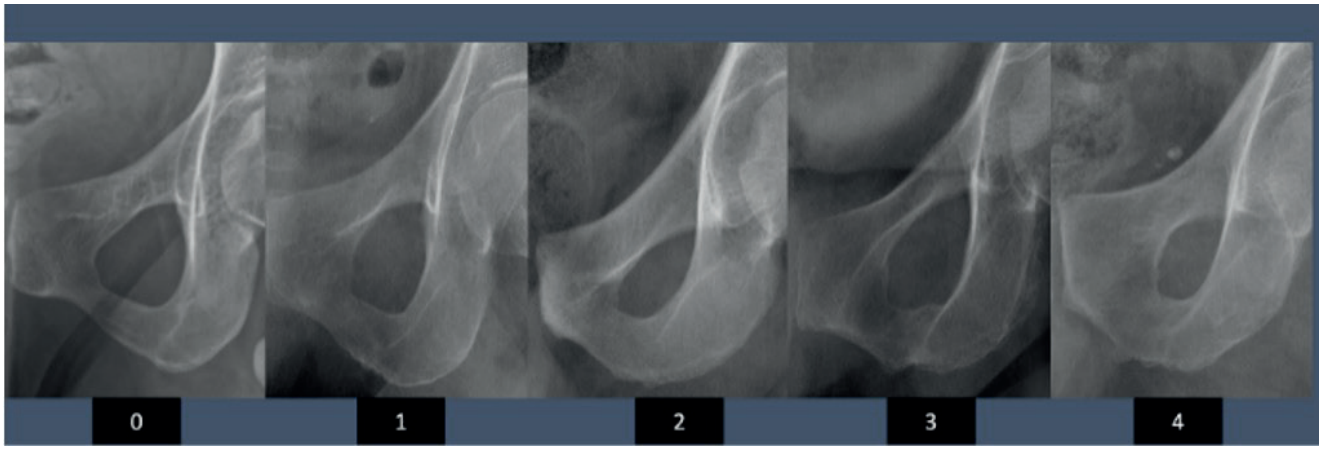

Figure 2. Grading example for ischium

the left side only 3 (3.3) patients had grade 1 major trochanter enthesopathy whereas no minor trochanter enthesopathy was identified.

When patients with and without clinically relevant pelvic enthesitis were compared, the proportion of females was significantly lower in the ≥ grade 2 group than in the < grade 2 group (53.3% vs 76.0%, p = 0.02), indicating a higher prevalence of males among patients with advanced entheseal involvement. Patients with ≥ grade 2 enthesitis were also older at the time of first pelvic radiography [44.4 (9.8) vs 40.6 (12.3)] years, p = 0.09) and at PsA diagnosis [42.2 (10) vs 37.9 (11.3) years, p = 0.06], although these differences did not reach statistical significance. Disease duration was comparable between groups (mean 2.2 years in both, p = 0.40).

A trend toward higher BMI was observed among patients with advanced enthesitis (BMI > 30 in 43.3% vs 26.2%, p = 0.09), and a positive family history of psoriasis or PsA was numerically more frequent (58.8% vs 38.9%, p = 0.17). Smoking history was similar between groups (52% vs 47%, p = 0.81). Clinically, dactylitis was slightly less common among patients with advanced enthesitis (23.8% vs 33.3%, p = 0.43), whereas a history of enthesitis was, as expected, more often recorded in this group (50% vs 38.2%, p = 0.47). On imaging, sacroiliitis according to the modified New York criteria was also more frequent in patients with ≥ grade 2 enthesitis (53.3% vs 41.8%, p = 0.29) (Table 1). Overall, both groups showed comparable findings in terms of disease activity parameters (**Table** 2).

3.2. Progression of pelvic entheseal involvement

After a mean (SD) follow-up duration of 38.6 (32) months, follow-up data were available for 48 patients. Among these, the most frequently used first-line b/tsDMARDs were adalimumab (45.8%, n=22), etanercept (20.8%, n=10), and certolizumab (16.7%, n= 8). For second-line treatment, adalimumab (18.8%, n =9), golimumab (10.4%, n=5), and certolizumab (8.3%, n=4) were the most commonly prescribed agents. In the third-line setting, etanercept (8.3%, n= 4), adalimumab (6.3%, n= 3), and golimumab or secukinumab (2.1%, n= 1 each) were the most frequently used. Use of biologic

Table 1. Demographic and clinical characteristic of patients at bDMARD initiation

	All patients n=108	Patients with < grade 2 enthesitis* (n=67)	Patients with >= grade 2 enthesitis ^ (n=30)	P value
Female gender, n (%)	74 (68.5)	51 (76)	16 (53.3)	0.02
Age at the time of first SIJ radiography, mean (SD), years	41.5 (11.6)	40.6 (12.3)	44.4 (9.8)	0.09
Age at the time of first bDMARD initiation, mean (SD), years	41.5 (11.7)	40.5 (12.3)	44.4 (9.8)	0.09
PsA diagnosis age, mean (SD), years	39.1 (11.2)	37.9 (11.3)	42.2 (10)	0.06
PsA disease duration, mean (SD), years	2.2 (3.7)	2.2 (4.1)	2.2 (2.9)	0.40
PsO/PsA family history, n (%)	24 (40)	14 (38.9)	10 (58.8)	0.17
BMI > 30, n (%)	33 (31)	17 (26.2)	13 (43.3)	0.09
Smoking (ever), n (%)	43 (51.8)	24 (47)	12 (52)	0.81
Dactylitis (ever), n (%)	21 (30)	14 (33.3)	5 (23.8)	0.43
Entheisitis (ever), n (%)	23 (43.4)	13 (38.2)	6 (50)	0.47
Nail involvement, n #	28	13	11	NA
Sacroileitis according to mNY criteria, n (%)	49 (45.4)	28 (41.8)	16 (53.3)	0.29

*patients with at least one entheseal site is scored less than grade 2
^ patients with at least one entheseal site is scored grade 2 or more
In 11 patients, all of the entheseal sites were scored missing
The rest of the cases other than positive ones were missing and for this reason percentages were not provided
SIJ: Sacroiliac joint, bDMARD: biologic disease modifying anti-rheumatic drugs, BMI: Body mass index, PsA: Psoriatic arthritis, PsO: Psoriasis, mNY: Modified new york

Table 2. Disease activity parameters of patients at bDMARD initiation

	All patients n=108	Patients with < grade 2 enthesitis* (n=67)	Patients with >= grade 2 enthesitis ^ (n=30)	P value
BASDAI, mean (SD)	5.6 (2.0)	5.4 (2.0)	5.9 (2.0)	0.25
BASFI, mean (SD)	3.5 (2.2)	3.5 (2.4)	3.3 (2.1)	0.81
DAS-28, mean (SD)	3.6 (1.0)	3.6 (1.0)	3.8 (1.0)	0.22
DAPSA-28, mean (SD)	17.8 (6.8)	16.9 (5.8)	19.6 (7.9)	0.19
CRP, mean (SD)	1.2 (1.7)	1.0 (1.1)	1.5 (2.5)	0.13
HAQ-DI, mean (SD)	0.6 (0.5)	0.6 (0.5)	0.7 (0.5)	0.28

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index DAS-28, Disease Activity Score-28; DAPSA: the Disease Activity Index for Psoriatic Arthritis, CRP, C-reactive protein (mg/dl), HAQ-DI, Health Assessment Questionnaire Disability Index
*patients with at least one entheseal site is scored less than grade 2
^ patients with at least one entheseal site is scored grade 2 or more
In 11 patients, all of the entheseal sites were scored missing

agents beyond the third line was uncommon, with only a few patients receiving a fourth (n = 3) or fifth (n = 1) b/tsDMARD. In these later treatment lines, golimumab, secukinumab, tofacitinib, and infliximab were each used in a single patient.

Regarding radiographic progression, a one-grade increase in ischial enthesopathy was observed in 28% of patients, whereas progression beyond one grade was not seen. At the symphysis pubis, 8.5% of patients showed a one-grade and 3% a two-grade progression. On the right iliac wing, 6% of patients demonstrated a one-grade increase, with no progression exceeding one grade. On the left iliac wing, a one-grade progression was observed in 3% of patients, with no further increase beyond that level (Figure 3). No progression was detected at the greater or lesser trochanter sites

4. Discussion

This study presents a radiographic assessment of pelvic/hip entheseal involvement in patients with PsA, emphasizing both its frequency and longitudinal

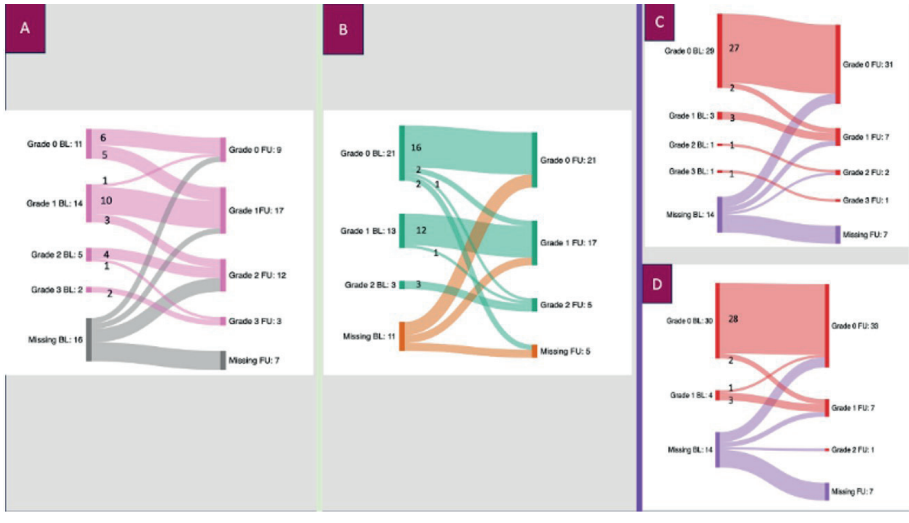

Figure 3. Changes of entheseal involvement of pelvic region A: Ischium (bilateral), B: Symphisis Pubis (bilateral), C: Iliac wing (right), D: Iliac wing (left), BL: Baseline, FU: Follow-up

changes. The bilateral ischium emerged as the most frequently affected sites, followed by the symphysis pubis, while iliac wing and trochanteric involvement were less common. Over a mean follow-up period of approximately three years, radiographic progression of pelvic entheseal lesions appeared limited, suggesting that structural damage in these regions tends to evolve slowly in a bDMARD population.

In a previous study comparing patients with PsA and rheumatoid arthritis (RA), Bitik et al. reported that radiographic ischial entheseal lesions were present in 50% of PsA patients, significantly higher than in RA. The frequency observed in our cohort was somewhat lower than the 50% reported by Bitik et al., which may be explained by differences imaging indication and methodologic differences in reporting [3]. Radiographs in the earlier study were obtained from patients with axial or heel pain, and this selection criteria may have increased the rates. Furthermore, no grading system was applied in that assessment, and the authors recorded cortical erosions and enthesophytes while excluding suspected cortical irregularities, making direct comparison with our findings difficult. In the CASPAR substudy assessing psoriatic spondylitis, Helliwell et al. reported slightly higher frequencies of advanced (grade 3-4) entheseal changes at comparable pelvic sites (ischial enthesitis 22%, symphysitis 25%, and iliac enthesitis 4%) [4]. This higher prevalence may be explained by the characteristics of their cohort, which included patients with longer disease duration, which has been shown previously in axial spondyloarthritis population, and predominantly axial involvement, as reflected by the high proportion of individuals with severe sacroiliitis (grade 3–4 in 82%) [4,5].

Nevertheless, in our study, the mNY criteria positivity reached up to 45% which is higher than expected in a general PsA cohort [6]. However, this should be kept in mind that these are patients who had pelvis radiography taken around bDMARD start. This may reflect particular patient population at risk of axial symptoms even there is not an inclusion criteria.

When comparing patients with and without clinically significant pelvic enthesitis, several patterns emerged that are consistent with prior observations on sex and mechanical load-related differences in entheseal disease. The lower proportion of females and the trend toward older age in the ≥ grade 2 group suggest that mechanical factors may contribute to entheseal structural damage, in line with prior studies linking entheseal new bone formation to cumulative biomechanical stress and male predominance [2,7]. The observed trend toward higher BMI among patients with advanced enthesitis supports this interpretation, as obesity is known to increase entheseal load and has been associated with greater entheseal thickness and structural change on imaging

The higher, though non-significant, frequency of positive family history of psoriasis or PsA in the advanced enthesitis group may reflect a genetic predisposition influencing entheseal response to inflammation or mechanical stress. It has already been shown that HLA-B27 positivity is associated with the presence of clinical enthesitis and also correlated with higher sonographic enthesitis scores, suggesting that this genetic background may predispose to more severe entheseal inflammation within limitation of HLAB27 is not reported in this assessment [8,9].

In our cohort, progression of entheseal structural changes was very limited, which may, at least in part, be related to the use of bDMARD therapy; however, this interpretation should be made with caution, as the study lacked a comparator group of patients not receiving biologic treatment or treated only with csDMARDs. This observation after all, aligns with previous data suggesting that bDMARDs can positively influence bone metabolism in PsA. Simon et al. demonstrated, using high-resolution peripheral quantitative CT, that PsA patients treated with bDMARDs exhibited significantly higher bone mineral density and improved bone strength compared with those receiving methotrexate or no DMARDs, indicating a direct effect of cytokine blockade on restoring bone homeostasis by reducing osteoclast activity and enhancing bone formation [10]. However, while these findings underscore the beneficial impact of biologic therapies on overall bone structure, their specific effects on entheseal sites remain insufficiently characterized. Supporting this, Mathew et al. reported that clinical enthesitis resolved in up to 86% of PsA patients treated with DMARDs within one year, yet highlighted the lack of imaging-based data to evaluate structural outcomes at the entheses [11]. Overall, the potential protective, or even regressive, effects of bDMARD therapy on structural entheseal lesions warrant further investigation.

This study has several limitations. First, the association between pelvic entheseal lesions and spinal structural damage was not explored, which has been previously shown in axSpA. Second, radiographs were scored by a single experienced reader, which may introduce observer bias despite the reader's more than 20 years of expertise in musculoskeletal imaging. Third, the cohort represents a selected population of PsA patients undergoing bDMARD initiation, and therefore, the results may not be generalizable to all PsA patients, Finally, the potential contribution of these lesions to axial pain could not be assessed, as systematic evaluation of symptom–imaging correlation was beyond the study scope. Despite these limitations, the study also has important strengths. To our knowledge, this is the first study to systematically evaluate radiographic progression of pelvic entheseal lesions over time in PsA. The inclusion of longitudinal imaging data provides valuable insight into the structural evolution of entheseal involvement in the context of biologic therapy.

To conclude, in a bDMARD cohort, pelvic/hip entheseal lesions were seen frequently. Patients with male gender is more commonly affected as well as the obese and older patients with family history had tendecy to be more commonly afffected. The progression on the contrary is very limited over 3 years and mainly seen at ischium.

Author contributions

Conception and design: G.A., A.S., L.K., U.K.; Data acquisition: G.A., A.S., L.K., U.K.; Data analysis: G.A., U.K.; Data interpretation: G.A., A.S., L.K., U.K.; Drafting of the manuscript: G.A.; Critical revision of the manuscript: G.A., A.S., L.K., U.K. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Ethics Committee of the Hacettepe University Faculty of Medicine (Date: August 23, 2022, Decision/Protocol No: 2022/13-19 KA-22005). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

Retrospective analysis of quality of life after trans-sacral epiduroscopic laser neural decompression for chronic back pain

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Abstract

Objective: Low back pain is a common health problem that most adults experience at least once in their lifetime and significantly impacts healthcare costs, workforce productivity, and overall quality of life. Trans-Sacral Epiduroscopic Laser Neural Decompression (ELND) is a minimally invasive technique often used for patients with lumbar disc herniation. ELND offers advantages such as shorter operation times, faster recovery, and continuous communication with the patient during the procedure which reduces the risk of accidental nerve damage. We aimed to analyze the effects of ELND on pain and quality of life.

Materials and Methods: A cohort of 89 patients diagnosed with lumbar disc herniation underwent the ELND procedure. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) was used to evaluate the quality of life of 89 patients before and six months after the ELND procedure.

Results: The analysis established a statistically significant increase in general health perception, physical functioning, physical role limitation, social functioning, vitality, pain, and general mental health subscales of the SF-36 questionnaire. However, the score for role limitation due to emotional problems decreased post-procedure. The median scores for general health perception increased from 54.3 to 68.3, physical functioning from 45.0 to 65.0, and pain from 10.6 to 63.0, among other subscales. The greatest improvement was observed in the physical role difficulty subscale.

Conclusion: As a result, the ELND procedure is an effective treatment for patients with chronic low back pain, as demonstrated by significant reductions in pain scores and improvements in patient-reported quality of life. Specifically, the study found statistically significant enhancements in general health perception, physical functioning, physical role limitation, social functioning, vitality, and general mental health six months after the procedure. These findings indicate that ELND not only alleviates pain but also contributes to better physical mobility, daily functioning, and overall well-being.

Keywords: low back pain, quality of life, psychological well-being, failed back surgery syndrome, YAG lasers, health survey

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This study was derived from the medical residency thesis of İskender Karakulak, titled "Retrospective evaluation of quality of life in patients with low back pain who received trans-sacral epiduroscopic laser decompression", conducted under the supervision of Altan Şahin at Hacettepe University, Faculty of Medicine, in 2016.

Introduction

Low back pain (LBP) is among the most prevalent musculoskeletal disorders worldwide and represents the leading cause of disability across age groups. Most adults experience LBP at least once in their lifetime, and a substantial proportion develop chronic symptoms. Globally, more than 600 million individuals are affected by activity-limiting LBP, resulting in significant healthcare costs, reduced productivity, and impaired quality of life [1,2]. The etiology of LBP is multifactorial, encompassing mechanical and non-mechanical causes. Mechanical sources include lumbar disc herniation, facet joint disease, spinal stenosis, spondylosis, and discogenic pain, while non-mechanical causes include inflammatory conditions, infection, and malignancy. Despite extensive diagnostic evaluation, most of the patients are classified as having "non-specific LBP" [3]. Among identifiable causes, lumbar disc pathology remains a major contributor to chronic LBP and associated disability [4]. Chronic LBP is frequently recurrent and persistent, substantially limiting physical function, social participation, and overall well-being [5]. Conservative management, including pharmacological therapy, physical rehabilitation, and lifestyle modification remains the first-line approach and is effective for many patients. However, a subset of individuals with refractory symptoms may benefit from interventional pain management strategies tailored to the underlying pathology. These interventions include epidural injections, transforaminal approaches, facet joint procedures, radiofrequency ablation, intradiscal therapies, and neuromodulation techniques.

Epiduroscopy is a minimally invasive percutaneous procedure that enables direct visualization of the epidural space and targeted treatment of pathological findings. With advancements in endoscopic and laser technologies, epiduroscopy has evolved from a diagnostic tool to a therapeutic modality. Trans-sacral epiduroscopic laser neural decompression (ELND) allows decompression of disc pathology and epidural adhesiolysis via a caudal approach. The technique offers several advantages, including avoidance of general anesthesia, shorter procedural and recovery times, and continuous patient feedback during the intervention, which may reduce the risk of neural injury [6]. Reported clinical success rates for ELND in lumbar disc herniation range from 60% to 80% [7,8].

Given the multidimensional burden of chronic LBP, evaluation of treatment outcomes should extend beyond pain intensity to encompass health-related quality of life. The 36-Item Short Form Health Survey (SF-36) is a validated and widely used instrument assessing physical, emotional, and social health domains [9-11], with established reliability and validity in the Turkish population [12-14]. The present study aimed to evaluate the impact of ELND on health-related quality of life by comparing SF-36 subscale scores before and six months after the procedure in patients with chronic low back pain, including selected cases of failed back surgery syndrome.

MATERIALS AND METHODS

In this retrospective study, SF-36 quality of life survey was utilized in 89 patients who were diagnosed with lumbar disc herniation and underwent ELND procedure to evaluate the changes before and 6 months after the procedure, and their quality of life was evaluated.

This study was conducted at Hacettepe University Faculty of Medicine, Department of Anesthesiology and Reanimation, Pain Clinic, Ankara. Permission from Hacettepe University Clinical Research Ethics Committee was obtained with project registration GO 16/312 and number 16969557-587 for the study.

Interventional procedures for low back pain are routinely performed in the institution. Patients who underwent the ELND procedure for chronic low back pain after examination, and who answered the SF-36 survey with a face-to-face interview technique before and 6 months after the procedure, were included in the study. The parts that the patients did not understand about the questions were explained to them by the interviewer. The answers were filled in by the patients.

Patients were included in the study if they were diagnosed with lumbar disc herniation associated with chronic low back pain, were deemed suitable candidates for trans-sacral epiduroscopic laser neural decompression after comprehensive clinical and radiological evaluation and underwent the ELND procedure at the study institution. Eligible patients were required to have chronic symptoms refractory to conservative management, including pharmacological treatment and physical therapy, and

to have completed the SF-36 questionnaire through face-to-face interviews both before the intervention and at six months post-procedure. Patients with failed back surgery syndrome (FBSS) were included in the study provided that they met the predefined clinical and procedural eligibility criteria. In the context of this study, FBSS was defined as the persistence or recurrence of chronic low back pain and/or radicular lower extremity pain following one or more lumbar spine surgical interventions, in the absence of a clear indication for repeat open surgery and after failure of adequate conservative management. Patients with a history of lumbar spine surgery who continued to experience symptoms attributable to epidural adhesions, recurrent or residual disc pathology, or nerve root irritation were considered eligible for ELND and therefore included in the cohort. Conversely, patients with postoperative pain caused by conditions requiring revision surgery, such as gross spinal instability, progressive neurological deficits, active infection, or malignancy, were excluded. This operational definition allowed FBSS patients to be evaluated alongside surgery-naive patients with chronic lumbar disc herniation, reflecting real-world clinical practice in which ELND is used as a minimally invasive treatment option for selected cases of refractory pain, including FBSS.

Patients were also excluded if they had incomplete SF-36 data, declined follow-up assessment, or had conditions that could confound quality-of-life evaluation, such as active spinal infection, malignancy, severe spinal instability requiring open surgery, or significant neurological deficits necessitating urgent surgical intervention. Additional exclusion criteria included inability to comprehend or reliably complete the questionnaire and the presence of severe psychiatric disorders that could independently impair emotional or functional assessment. These criteria were applied to ensure a relatively homogeneous cohort and to allow a focused evaluation of the impact of ELND on pain and health-related quality of life.

The quality-of-life scores of each subscale were compared before and 6 months after the procedure.

Intervention Technique

The patients were in supine position, monitored anesthesia care was utilized during the interventions. Under sterile setting, a guide needle was inserted through the sacral hiatus and local anesthesia of the sacral hiatus was achieved. With the help of fluoroscopic imaging. a guide wire was sent through the needle, the needle was withdrawn, and the wire was removed after sending a 9F introducer trocar over the guide wire. A fiberoptic endoscope was projected through the introducer, and the target disc was approached with fluoroscopic guidance. The level of adhesion was determined by administering radiopaque (Figure 1). The protruded discs were degraded with Yttrium-Aluminum oxide Garnet (YAG) laser which was inserted through the endoscope. YAG laser was tested by 0.5 joule 0.5 Hz, and protruded disc was shrunk by a YAG laser of 0.8 J, 0.8 Hz until the sufficient decompression of the nerve root was achieved. Adhesions were removed both mechanically and with YAG laser. Direct visualization of the widening of the epidural space through the epiduroscope was observed and finally, the radiopaque

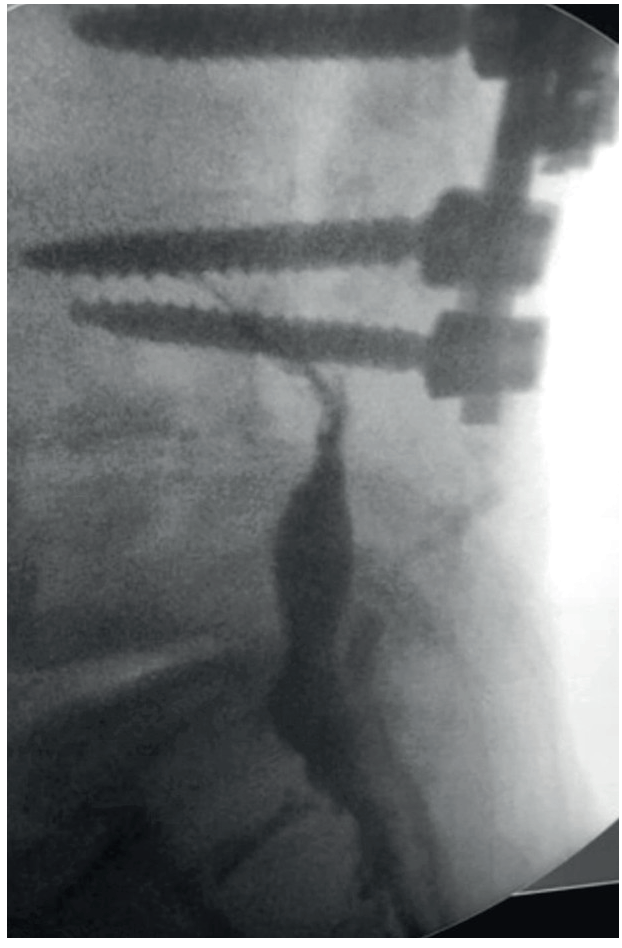

Figure 1. Determining the point at which the contrast cannot access past adhesion before performing adhesiolysis

substance was administered once more, before the procedure was terminated. The passage of the contrast substance across the adherent area and further caudal passage was visualized (Figure 2). A 10 mL of solution mixture of normal saline and dexamethasone, was injected into the epidural space at the end of the procedure. Patient screening, assesment, inclusion and exclusion criteria and follow-up is demonstrated in the flow diagram (Figure 3).

Statistical Analysis

The data obtained from the patient surveys were analyzed utilizing IBM-SPSS Statistics program (version 23.0 IBM International Business Machines Inc. Armonk, NY, USA). Frequency and percentages were used for presenting categorical variables, and median with range were used for non-categorical variables in descriptive statistics. The Wilcoxon Signed Rank Test was used to compare the changes of quantitative parameters that do not present normal distribution. In statistical decisions, $p<0.05$ was considered as significant. All hypotheses were established and tested bi-directionally.

RESULTS

The cohort consisted of 89 patients (63 female and 26 male). The mean age of the patients was 54.7 ± 16.4 years. The oldest patient participating in the study was 96 years old and the youngest was 17 years old.

The difference between pre- and post-procedure scores in all subscales was found to be statistically significant. When comparing the mean SF-36 scores before and after the procedure across all subscales, the following average increases were observed: 14 points in general health perception, 15.4 points in physical functioning, 41 points in physical health - role limitation, 44 points in social functioning, 16 points in vitality, 52.4 points

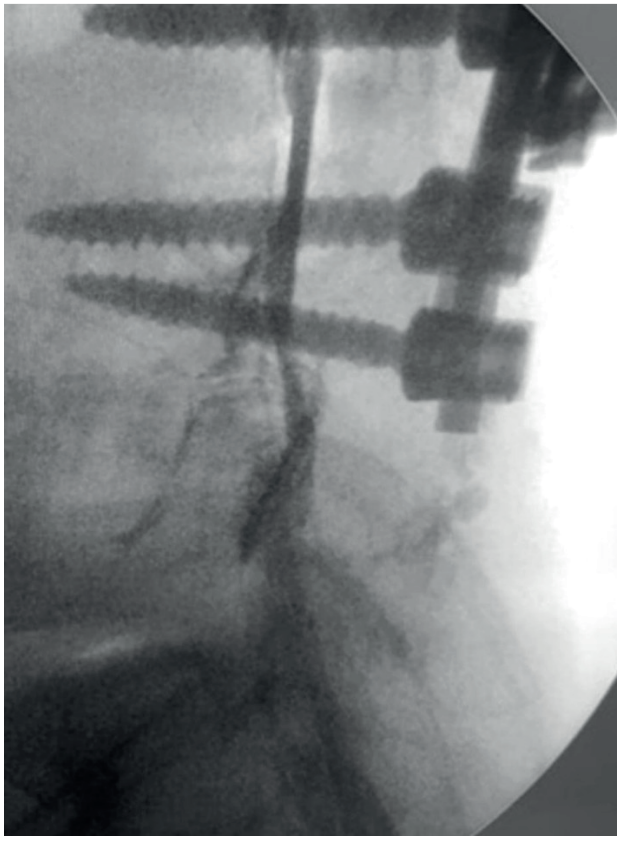

Figure 2. Visualization of the opaque rising to higher levels after adhesiolysis

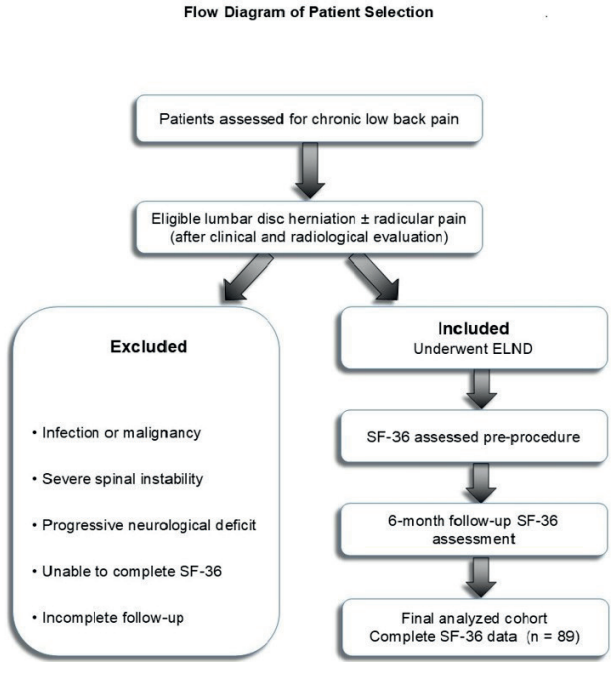

Figure 3. Flow diagram illustrating patient screening, eligibility assessment, inclusion and exclusion criteria, follow-up, and final analysis.

Patients with chronic low back pain, including selected cases of failed back surgery syndrome (FBSS), were evaluated for eligibility for trans-sacral epiduroscopic laser neural decompression (ELND). Only patients with complete pre- and post-procedural SF-36 data at six months were included in the final analysis.

in pain, 24.7 points in general mental health The pre-intervention median general health perception score was 54.3, which increased to 68.3 after the procedure. Physical functioning scores significantly increased from 45.0 to 65.0, and physical role limitation scores rose remarkably from 11.0 to 52.0. Improvements were also noted in social functioning (from 27.9 to 71.9), vitality (from 19.0 to 60.0), pain (from 10.6 to 63.0), and general mental health (from 50.6 to 75.3). Interestingly, emotional role limitation scores decreased from 67.7 to 60.0, which was the only subscale that did not show post-intervention improvement. Overall, a 5-point decrease in SF-36 score was observed (Table 1).

DISCUSSION

Low back pain is a notable health problem that may affect 85% of society at least once in their lifetime and may lead to increased expenditures in terms of diagnosis and treatment costs, as well as the workforce losses [15]. Usually, low back pain that lasts more than 3 months is considered chronic. Chronic low back pain, which is the second most common complaint of pain in people under the age of 45, significantly affects the quality of life due to its persistent and debilitating nature.

Instability occurs after lumbar spine procedures due to decompression and facet resection, even in simple discectomy operations without fusion. Therefore, as in failed back syndrome, recurrent surgeries involve higher risks [16]. As a result of the widespread use of imaging systems and the development of smaller endoscopes, epiduroscopy has begun to take its place among the treatment methods as a minimally invasive procedure. Although the epiduroscope was used initially only for imaging and opening epidural adhesions, with the development of laser probes, it can now also be used for epiduroscopic discectomy. Trans-Sacral Epiduroscopic Laser Decompression (ELND) procedure is being performed in our institution on eligible patients with chronic low back pain and unsuccessful back surgery.

This study aimed to evaluate the impact of the ELND procedure on the quality of life of patients suffering from chronic low back pain through the SF-36 survey, which assesses various health-related quality of life dimensions. In this study, the SF-36 quality of life survey was administered to 89 patients who underwent the ELND procedure to assess changes in their quality of life before and six months after the procedure. The demographic data of the participants show that 63 of the 89 patients (71%) were female and 26 (29%) were male. Other studies demonstrate that women are more likely than men to seek primary or tertiary care for chronic low back pain, indicating that men are less likely to use healthcare services and more likely to engage in negative health behaviors, such as ignoring pain and other health-related symptoms, compared to women [17]. For example, Lee et al. performed epiduroscopic laser decompression on patients with lumbar spinal stenosis and found that 53% were female [18]. Similarly, a study by Jo et al. reported a female rate of 61% [8].

The SF-36 quality of life survey, administered to patients, evaluates 8 subscales. In a study by Járomi et al., patients with chronic low back pain showed low scores across all subscales of the SF-36 test [19]. Similarly, Derby et al. found that patients with chronic low back pain had low scores on the SF-36 test [20]. In our study, patients also

Table 1. Short Form-36 subscales before and after ELND intervention

SF-36 Subscales	Pre-Intervention	Post-Intervention 6th week	Significance
General Health Perception	54.3 (40-70)	68.3 (55-85)	p<0.05
Physical Functioning	45.0 (5-80)	65.0 (15-90)	p<0.001
Role Limitation - Physical Health	11.0 (0-25)	52.0 (0-100)	p<0.001
Role Limitation - Emotional Problems	67.7 (0-100)	60.2 (33-100)	p<0.01
Social Functioning	27.9 (12.5-37.5)	71.9 (37.3-87.5)	p<0.01
Vitality	19.0 (0-35)	60.0 (35-85)	p<0.001
Pain	10.6 (0-22)	63.0 (41-80)	p<0.001
General Mental Health	50.6 (36-72)	75.3 (64-84)	p<0.001

Scores, Mean (range)

received low scores in all subscales of the SF-36 test conducted before the procedure. These results indicate that chronic low back pain significantly reduces quality of life.

Several studies have evaluated the outcomes of patients who underwent ELND for chronic low back pain, but none of these studies used the SF-36 scale. Instead, they utilized measures such as the Visual Analog Score (VAS) and the Oswestry Disability Index (ODI) [8,21]. For instance, in the study by Mumcu et al., it was reported that the VAS and ODI scores of patients with lumbar disc herniation decreased on the first postoperative day following the ELND procedure [21]. Similarly, in the study by Lee et al. involving patients with lumbar spinal stenosis, VAS scores were evaluated at 1, 3, and 6 months, as well as one and two years after the procedure, revealing a decrease in VAS scores over time. [18].

In the study by Jo et al., the symptoms of patients who underwent epiduroscopic laser decompression were evaluated using a 5-point scale: 5 (very good), 4 (good), 3 (no change), 2 (bad), and 1 (very bad). The survey was administered before the procedure, and then again at 2 weeks and 1-month post-procedure. It was reported that patients experienced symptom relief after the procedure [8]. These findings suggest that the ELND procedure for chronic low back pain is an effective and reliable treatment method that not only reduces pain but also improves the functional and psychological status of patients. In our study, we observed an increase in all subscales of the SF-36 quality of life scale following the ELND procedure.

In the general health perception subscale, efforts were made to determine patients' personal perception of their overall health. Recognizing that diseases are intertwined with personal and social contexts, which influence every aspect of health, we utilized quality-of-life measures to contextualize this understanding. Our study revealed a notable enhancement in patients' health perception within this subscale.

The physical functioning subscale primarily addresses daily physical activities. Our study indicated a significant improvement in patients' daily life dynamics and, consequently, their quality of life as reflected in this subscale. This data gains further significance when we consider the role of chronic low back pain contributing to overall workforce impairment [15]. The physical health role limitation subscale assesses the impact of physical issues on tasks like work or school. Given the relevance of chronic low back pain to workforce loss, our study found a marked increase in physical role limitation score.

Emotional role limitation examines whether emotional issues affect work or daily activities. Although our study showed an average decrease in emotional role difficulties, overall scores saw a general increase.

Social functioning scores significantly improved post-procedure compared to pre-procedure levels, indicating enhanced social integration following treatment. Vitality, measuring a person's energy and passion for life, notably increased in our study, indicating enhanced vitality among participants.

The pain subscale assesses the presence and impact of pain. Higher scores on the SF-36 pain subscale indicate reduced pain perception and, consequently, an improved quality of life for patients. Participants reported an increase in pain scores post-procedure in our study. An increase in SF-36 pain scores, indicating reduced pain perception, was observed following the ELND procedure. This finding aligns with findings from Mumcu et al., who utilized VAS and ODI scores to document significant pain reduction [21]. A decrease in pain was observed in various other studies utilizing different scoring systems [8,18].

The general mental health subscale evaluates feelings of calmness, happiness, and comfort. Our study observed a statistically significant improvement in mental health indicators.

In our study, although there was an average decrease in emotional role difficulties, there was an overall increase in SF-36 scale following the ELND procedure indicating an increase in the overall quality of life of patients with chronic low back pain. The findings of this study align with previous research indicating that minimally invasive procedures, such as ELND, provide substantial improvements in patients' quality of life. The significant enhancements in physical functioning, general health perception, and social functioning suggest that ELND not only addresses the physical pain but also positively affects patients' overall well-being.

One notable finding was the decrease in the emotional role limitation subscale, indicating that while physical

aspects of health improved, some emotional challenges remained or worsened post-intervention.

An unexpected finding of the present study was the modest but statistically significant decrease in the SF-36 emotional role limitation subscale despite clear improvements in pain, physical functioning, social functioning, vitality, and general mental health. This apparent contradiction may reflect the complex and multifactorial nature of emotional well-being in patients with chronic low back pain. Although ELND effectively alleviates nociceptive input and improves physical capacity, emotional role functioning is strongly influenced by persistent psychosocial stressors, such as work-related pressures, financial concerns, caregiving responsibilities, and long-standing maladaptive coping strategies that may not be resolved in parallel with pain reduction. In addition, patients may experience heightened emotional awareness or increased expectations for rapid psychosocial recovery following a successful intervention; when these expectations are unmet, perceived emotional role functioning may transiently decline. Previous studies evaluating chronic low back pain populations have emphasized that emotional and psychological outcomes are less directly correlated with procedural pain relief than physical domains and are often shaped by depression, anxiety, pain catastrophizing, and social context [19,20]. Similarly, studies of minimally invasive spinal interventions using measures other than SF-36 have reported substantial pain and functional improvements without uniform gains in emotional outcomes. Clinically, these findings underscore the importance of adopting a biopsychosocial approach: interventional pain procedures such as ELND may need to be complemented by psychological assessment, patient education, and, when appropriate, targeted psychosocial or behavioral interventions to optimize emotional role functioning and achieve more holistic recovery.

The limitations of this study include its retrospective design and the lack of a control group, which may affect the generalizability of the findings. Future research with larger sample sizes and randomized controlled designs are recommended to further validate these findings and explore the long-term outcomes of ELND on quality of life.

Low back pain is a significant health problem that most adults experience at least once in their lifetime. It is common and can result in increased costs due to diagnosis and treatment, as well as a decline in quality of life and productivity.

There was a statistically significant improvement in all subscales of the SF-36 quality of life survey after the ELND procedure, except for emotional problems.

In conclusion, the ELND procedure appears to be an effective minimally invasive treatment option improving the quality of life in patients with chronic refractory low back pain and/or lower extremity pain, comprising conditions such as lumbar disc herniation, lumbar stenosis, and failed back surgery syndrome that do not respond to conservative treatment. Our study indicates that the ELND procedure not only alleviates pain but also enhances the quality of life for patients with chronic low back pain. The significant improvements in various SF-36 subscales indicate that ELND may enhance physical, social, and mental health aspects. However, the observed decline in the emotional role limitation subscale suggests the necessity of addressing emotional health in conjunction with physical treatment to achieve holistic patient care.

Author contributions

Conception: İ.K., N.Ç., A.Ş.; Design: İ.K., Ç.Y., M.A.S., N.Ç., A.Ş.; Data acquisition: İ.K., Ç.Y.; Data analysis: M.A.S.; Data interpretation: İ.K., Ç.Y., M.A.S., N.Ç., A.Ş.; Drafting of the manuscript: İ.K., M.A.S., A.Ş.; Critical revision of the manuscript: Ç.Y., M.A.S., A.Ş. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Clinical Research Ethics Committee (Date: March 22, 2016, Decision/Protocol No: project registration GO 16/312 and number 16969557-587). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

The investigation of the inflammation hypothesis in children diagnosed with ASD and ADHD using complete blood count variables

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Abstract

Objective: This study aims to compare the inflammation-related complete blood count (CBC) variables in children diagnosed with Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD).

Materials and Methods: Retrospective data on CBC values and Childhood Autism Rating Scale (CARS) scores for 30 children with ASD and 30 with ADHD, aged 60-108 months, were retrieved from hospital automation systems. Inflammatory-related CBC parameters, including hemoglobin (Hb), red cell distribution width (RDW), neutrophil, lymphocyte, monocyte, and platelet counts, mean cell volume (MCV), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), were compared between the two diagnostic groups. This study has a retrospective and cross-sectional design.

Results: Children with ASD exhibited significantly higher platelet counts ($p=0.003$; $t=3.052$; $d=0.788$) and PLR ($p = 0.044$; $Z = -2.011$; $r = 0.259$), whereas MPV was significantly lower ($p=0.029$; $t=-2.241$; $d=-0.579$) compared to children with ADHD. No significant differences were observed in other parameters. Additionally, a negative correlation was identified between CARS scores and RDW values in children with ASD ($p = 0.035$, $r = -0.387$).

Conclusion: Although ASD and ADHD are two neurodevelopmental disorders in which inflammation has been investigated in their pathophysiology, the inflammatory processes may differ between the two conditions. Future genetic and biochemical studies related to platelets in ASD may provide further insights into this area.

Keywords: autism, attention deficit hyperactivity disorder, inflammation, PLR, MPV

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are two neurodevelopmental disorders. Although multifactorial genetic factors are believed to play a role in the etiology of both conditions, the importance of gene-environment interactions is also emphasized [1,2]. Environmental factors suggested to play a role in etiology include prenatal maternal inflammation, systemic inflammation in the individual, and neuroinflammation. Some studies have shown that individuals diagnosed with ASD and ADHD exhibit an increase in certain inflammation-related cytokines [3,4]. On the other hand, due to their cost-effectiveness and minimally invasive nature, analyzing certain inflammation-related parameters in peripheral blood has recently gained prominence. Various studies have demonstrated that parameters easily obtained from a complete blood count, such as neutrophil, monocyte, lymphocyte

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counts, and neutrophil/lymphocyte ratio (NLR), differ in neurodevelopmental disorders compared to healthy controls, similar to findings in cardiovascular diseases, cancer, rheumatological conditions, and other illnesses [5,6].

To date, no consistent results have been obtained regarding any parameters derived from complete blood count in children diagnosed with ADHD and ASD. Nevertheless, a significant increase in NLR has been reported in many studies for both disorders compared to controls [5,7]. However, studies also report no such difference, and some even report lower NLR levels [8-10]. In addition to NLR, variables such as neutrophil, lymphocyte, monocyte counts, mean platelet volume (MPV), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have also been shown to differ in children diagnosed with ASD and ADHD compared to healthy controls [11,12].

Differences related to NLR are explained in terms of immune response and inflammation [13]. Additionally, the importance of platelet and platelet-related variables in neurodevelopmental disorders, compared to healthy controls, is highlighted [14,15]. For example, serotonin is emphasized as a significant shared product that functions as a neurotransmitter in the neuronal system, is secreted from the digestive system, and is stored in platelet granules. Several studies have reported increased serotonin levels in autism compared to healthy controls [16,17].

Variations in findings across previous studies on this topic may be attributed to differences in participant age groups, wide age ranges, and the cross-sectional nature of the measurements. In this study, based on the knowledge that blood cell parameters can vary with age, the age range was kept short [18]. Most literature compares individuals diagnosed with ASD and ADHD to healthy controls. However, studies directly comparing inflammation-related blood parameters between these two neurodevelopmental disorders are limited [5,19]. Despite both being neurodevelopmental disorders, considering the differences in their treatments, we hypothesize that these conditions may also differ in inflammation-related parameters. Additionally, based on past findings of platelet-related differences and hyperserotoninemia in ASD, we hypothesize that autism may involve a different inflammatory process than ADHD.

This study compares chronic inflammatory blood parameters in children aged 5–8 years with ASD and ADHD. We hypothesize that inflammation-related parameters will differ significantly between these disorders, with ASD patients displaying more prominent inflammatory markers than the ADHD group.

Materials and Methods

This study was designed as a retrospective, cross-sectional, and comparative analysis of children aged 60 to 108 months who were diagnosed with ASD and ADHD at Hacettepe University's Pediatric and Adolescent Psychiatry outpatient clinic between January 1, 2023, and January 1, 2025. Data collection was subsequently performed between September 15 and September 30, 2025, by screening the hospital's electronic automation system. The Childhood Autism Rating Scale (CARS) scores obtained during psychiatric assessment and complete blood count (CBC) results obtained by the pediatrician were also retrieved from the hospital automation system.

The diagnoses of ASD and ADHD were made according to DSM-5 criteria during psychiatric evaluations. In the hospital automation screening, only patients with ASD and ADHD diagnoses who did not have a secondary psychiatric diagnosis were included in the study. Furthermore, participants were not using any psychotropic medication before. Patients with epilepsy, intellectual disability, organic brain injury, psychotic disorders, or acute or chronic physical illnesses, as well as those exhibiting abnormalities in CBC indicative of specific medical conditions, were excluded from the study.

CBC parameters, including hemoglobin (Hb), red cell distribution width (RDW), neutrophil count, lymphocyte count, monocyte count, platelet count, mean cell volume (MCV), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), were obtained.

The statistical analysis was performed using SPSS (version 31). The assumption of normality for numerical variables was examined using the Shapiro–Wilk goodness-of-fit test. Homogeneity of variances was analyzed using Levene's test. For numerical data, the independent two-sample t-test was used for normally

distributed variables, while the Mann–Whitney U test was used for non-normally distributed variables. Categorical variables are presented as numbers and percentages. The Pearson Chi-Square test was employed to analyze categorical variables. To evaluate the relationship between two continuous variables, Pearson's correlation was used for normally distributed variables, and Spearman's correlation was used for non-normally distributed variables. Effect sizes were calculated for each statistical test to assess the clinical significance of differences between the two means. The level of statistical significance was set at $p<0.05$.

Ethical approval for study number SBA 25/883 was granted by the Hacettepe University Health Sciences Research Ethics Committee on November 11, 2025, with decision number 2025/21-33.

Childhood Autism Rating Scale (CARS)

The CARS consists of 15 items, each rated on a half-point scale from 1 to 4. The scale is used to distinguish children on the autism spectrum from those with intellectual disabilities and to assess the severity of autism. It provides an objective and measurable evaluation based on direct observation of behaviors. The scale can be applied to children of all age groups, from preschool age onwards. Scores on the scale range from 15 to 60 points. Children who score below 30 do not exhibit autistic signs, those with scores between 30 and 36.5 are considered to have mild to moderate impairment, and those with scores from 37 to 60 are classified as having severe impairment [20]. The scale has been validated for Turkish language and culture, with studies demonstrating good validity and reliability [21].

Results

There was no significant difference in age and gender distribution between the ADHD and ASD groups ($p>0.05$). In the ADHD group, 27 males (90%) and 3 females (10%) were included, whereas in the ASD group, 23 males (76.7%) and 7 females (23.3%) were included. The median age in the ADHD group was 70.00 months (IQR: 14.75), whereas in the ASD group, the median age was 72.50 months (IQR: 15.75). The mean CARS score in the ASD group was 35.23 ± 5.24.

In this study, significant differences between the ASD and ADHD groups were observed exclusively in platelet-related parameters, specifically PLR, MPV, and platelet count. The median PLR was higher in the ASD group compared to the ADHD group [102.79 (48.10) vs. 84.62 (43.60)]. Similarly, the mean platelet count was significantly higher in children with ASD (349.80 ± 71.18) than in those with ADHD (295.73 ± 65.95). Conversely, the mean MPV was lower in the ASD group (7.72 ± 0.64) than in the ADHD group (8.14 ± 0.80). Statistical analysis confirmed significant differences for PLR (**p=0.044**, Z=-2.011, r=0.259), MPV (**p=0.029**, t=-2.241, d=-0.579), and platelet count (**p=0.003**, t=3.052, d=0.788). No other variables showed significant intergroup differences. Detailed comparisons of the complete blood profiles are presented in Table 1.

No significant correlation was found between CARS scores and variables such as hemoglobin, platelet count, neutrophil, lymphocyte, monocyte, MCV, MPV, NLR, MLR, and PLR among children with ASD ($p>0.05$). A moderate effect size negative correlation was observed between CARS scores and RDW (**p=0.035**, r=-0.387).

Discussion

In this study, the inflammatory markers in two neurodevelopmental disorders, ADHD and ASD, were investigated in children aged 5-8 years using complete blood count parameters, such as NLR and PLR, which have been reported in the literature as potentially useful for inflammation monitoring [5,13]. The results showed that children with ASD had higher platelet count and PLR values, and lower MPV values compared to children with ADHD. No significant differences were found between the two groups for other variables.

A significant portion of existing studies have reported that NLR and PLR ratios are significantly increased in patients diagnosed with both ASD and ADHD compared to healthy controls [7,22]. However, although the number of such studies is limited, some research has also shown that this difference in NLR or PLR is not observed in at least one of the two disorders [10,23]. Additionally, other studies have demonstrated that MLR, neutrophil count, and monocyte count are also higher in individuals with ADHD and ASD compared to healthy controls [12,24]. There are studies that report significantly higher platelet counts in both disorders

compared to healthy controls, as well as studies that report no significant difference [11,16,25-27].

The neuroinflammation hypothesis is one of the possible explanations proposed in the pathophysiology of ASD and ADHD, and many studies continue to investigate this area. For example, it has been suggested that cytokines such as interleukin-1β (IL-1β), interleukin-2 (IL-2), and interleukin-6 (IL-6) may play a role in ADHD, while cytokines like IL-6 and tumor necrosis factor alpha (TNF-alpha) may be involved in ASD [28,29]. The role of neutrophils in acute inflammation is already well known. It has been increasingly understood in recent decades that they also play an important role in chronic inflammation. The role of neutrophils has been demonstrated in many chronic diseases, including autoimmune and cardiovascular diseases [30]. For this reason, it is known that NLR ratios increase in various chronic diseases and are used to predict disease outcomes [6]. In studies on ADHD and ASD, a significant portion has shown that NLR values are higher in affected individuals compared to healthy controls [5,7]. However, some studies have reported no difference or lower values [8,10].

In our study, the lack of difference in NLR ratios between the two patient groups could be due to several factors. Although patients without additional psychiatric diagnoses were included based on hospital records, the absence of a structured diagnostic tool means there could be unidentified psychiatric comorbidities, such as tics and depression, which can affect NLR ratios [31,32]. Another possibility is that children with ASD may have been diagnosed and started treatment before the age of 5-8 years, leading to a decrease in ASD severity. Indeed, the relatively low mean CARS scores in children with ASD suggest that the severity of their condition is not high. Perhaps the interventions used for autism treatment have reduced inflammation severity neurobiologically through epigenetic mechanisms [33]. Longitudinal studies monitoring inflammation markers in individuals diagnosed with ASD and ADHD would be valuable to test these hypotheses.

In our study, we primarily found that variables related to platelets differ in children diagnosed with ASD and ADHD. More specifically, we observed that children with ASD had higher platelet counts and PLR values, while their MPV was lower. There are studies showing increased platelet counts and PLR values in studies involving children with both ASD and ADHD [16,23,25,34]. MPV levels are generally higher in children diagnosed with ADHD compared to healthy controls [11,27]. On the other hand, in studies involving children with ASD,

Table 1. Comparison of complete blood count parameters in children diagnosed with ASD and ADHD

	ASD	ADHD	Test statistic	p-value	Effect size
	Mean±SD Median (IQR)	Mean±SD Median (IQR)			
Hb (g/dL)	12.94±1.00	12.75±0.96	0.759^{t}	.451	0.196^{d}
RDW (%)	13.60 (1.70)	14.15 (1.01)	-1.450^{z}	.147	-0.187^{r}
Neutrophil (10^3/ul)	3.53±1.14	3.85±1.37	-0.990^{t}	.327	-0.256^{d}
Lymphocyte (10^3/ul)	3.56 (1.25)	3.55 (1.60)	-0.370^{z}	.711	-0.047^{r}
Monocyte (10^3/ul)	0.60±0.33	0.66±0.20	-0.404^{z}	.686	-0.052^{r}
Platelet (10^3/ul)	349.80±71.18	295.73±65.95	3.052^{t}	**.003***	0.788^{d}
MCV (fL)	79.30 (7.00)	78.25 (5.22)	-0.614^{z}	.539	-0.079^{r}
MPV (fL)	7.72±0.64	8.14±0.80	-2.241^{t}	**.029***	-0.579^{d}
NLR	1.06±0.51	1.20±0.66	-0.939^{t}	.352	-0.243^{d}
MLR	0.18 (0.08)	0.17 (0.15)	-0.274^{z}	.784	-0.035^{r}
PLR	102.79 (48.10)	84.62 (43.60)	-2.011^{z}	**.044***	-0.259^{r}

ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; Hb: hemoglobin; RDW: red cell distribution width; MCV: mean cell volume; MPV: mean platelet volume, NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio; Z: Z test value; t: t test value; d: cohen's d value; r: effect size value; *p<0.05.

MPV values have been found to be lower than those of healthy controls or show no significant difference [14,35]. The finding of lower MPV in children with ASD may reflect the production of smaller platelets following platelet activation induced by chronic inflammation. As such, the decrease in MPV should be interpreted not as a direct biomarker of ASD, but rather as a correlate of platelet activation dynamics during inflammation [36].

Studies related to platelet products in individuals with ASD are not entirely new [37,38]. Some studies have reported various abnormalities in platelet function related to ASD [14]. For example, these studies have suggested that there may be a relationship between hyperserotoninemia detected in the blood of ASD patients and platelet serotonin secretion, as well as overlaps in certain genetic expression profiles of neurons and platelets, which use similar signaling pathways [15,17]. On the other hand, platelets play an important role in inflammation together with neutrophils and influence each other's functions [39]. All these reasons highlight the need for further research investigating the relationship between platelet functions and ASD, especially in inflammation-related studies, at the genetic and biochemical levels.

The finding of a negative correlation between CARS scores and RDW in children diagnosed with ASD was contrary to expectations. In the literature, RDW values in children with ASD are generally reported to be similar to those of healthy children. Higher RDW values in ASD are typically associated with nutritional deficiencies resulting from selective eating behaviors or chronic inflammation. However, a low RDW value is not considered a pathological indicator; rather, it reflects a more uniform distribution of erythrocytes in the blood [40]. These unexpected results may be linked to variations in nutritional status, erythropoietic stability, or oxidative stress among participants with ASD [40]. It is also probable that measurement variability, along with our reliance on retrospective records and a relatively small cohort, influenced these outcomes.

Our study has some limitations. These include the retrospective collection of data from hospital records, which may lead to the omission of possible psychiatric comorbidities, the absence of a healthy control group, and the relatively small sample size due to the narrow age range of participants. Furthermore, because the study is based on retrospective data and lacks longitudinal follow-up, the findings should be interpreted as cross-sectional rather than causal. Even though our sample was limited to children without acute or chronic illnesses and no history of psychotropic use, inflammatory markers could still have been influenced by past medications, subclinical infections, or nutritional shifts. Not being able to control for these factors remains a limitation of this research.

Among the strengths of the study, it is noted that, given that hematological values vary across age groups, the age range of participants was kept narrow to ensure homogeneity. Additionally, instead of using a single inflammation marker such as NLR, multiple parameters were employed. Furthermore, the study compared inflammation markers in two neurodevelopmental disorders believed to contribute to neuroinflammation.

Conclusion

Although previous studies have shown that inflammation may play a role in both ASD and ADHD diagnoses, the number of studies comparing these two disorders is limited, and therefore, our study is expected to contribute to the literature. In this study, children diagnosed with ASD had significantly higher platelet counts and PLR values compared to children with ADHD, while MPV was found to be significantly lower. Based on our findings, we recommend conducting genetic and biochemical studies involving platelet-related parameters in inflammation research in ASD.

Author contributions

Conception and design: C.A., K.N., D.Ü.; Data acquisition: C.A., K.N., D.Ü., B.K.; Data analysis: C.A., B.K.; Data interpretation: C.A., K.N., D.Ü., B.K.; Drafting of the manuscript: C.A., B.K.; Critical revision of the manuscript: C.A., K.N., D.Ü.. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Health Sciences Research Ethics Committee (Date: November 11, 2025, Decision/Protocol No: 2025/21-33). Ethics committee approval and informed consent were not required for this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

Clinical and cytogenetic characteristics of patients with Triple X syndrome: Experience from a tertiary center

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Abstract

Background: Triple X syndrome is the most common sex chromosome aneuploidy in females; however, due to the subtlety of clinical findings, only a small proportion of affected individuals are diagnosed. This study presents the demographic, clinical, and cytogenetic characteristics of patients with Triple X syndrome followed at a single center.

Methods: We retrospectively reviewed the medical records of patients diagnosed with Triple X syndrome at our department between 2008 and 2025. Demographic characteristics, clinical findings including anthropometric measurements, dysmorphic features, associated anomalies, endocrine and neurodevelopmental findings, and cytogenetic results were analyzed.

Results: The study included a total of 20 patients diagnosed with Triple X syndrome, 13 of whom (65%) had a non-mosaic 47,XXX karyotype and 7 (35%) had mosaic chromosomal abnormalities. Four patients received a prenatal diagnosis, four were diagnosed in adulthood, and the remaining patients were diagnosed during childhood. Dysmorphic features; neurodevelopmental problems such as developmental delay, intellectual disability, and attention-deficit/ hyperactivity disorder; as well as cardiac defects and endocrine disorders were the main characteristics observed in the patients.

Conclusion: Triple X syndrome is a relatively common chromosomal disorder, which should be considered in patients who experience congenital anomalies, neurodevelopmental abnormalities, and reproductive problems. Variable and subtle findings should be carefully considered, bearing in mind that mosaic cases may present with diverse and overlapping phenotypes.

Keywords: Triple X syndrome, 47,XXX, sex chromosome aneuploidy, chromosome analysis

Introduction

Triple X syndrome (47,XXX) was first described in 1959 in a female patient presenting with absence of secondary sexual characteristics and primary ovarian failure, and was introduced as the third identified sex-chromosome abnormality, termed 'super-female', with the initial assumption that its manifestations were limited to the genital tract [1]. The incidence of this disorder has been estimated at about 1 per 1,000 females [2].

While the vast majority of patients do not exhibit significant phenotypic abnormalities or marked neurodevelopmental delay, the clinical spectrum is broad, with substantial variability in both manifestations and severity among individuals. Tall stature, minor dysmorphic features, congenital anomalies such as genitourinary malformations, and premature ovarian failure are among the commonly observed findings in affected individuals [2]. Neurodevelopmental problems are also frequently reported in this syndrome [2].

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The condition results primarily from nondisjunction occurring during maternal meiosis, predominantly during meiosis I [3]. The phenotypic features in affected individuals are thought to result from overexpression of genes that escape X-inactivation. Although 47,XXX is the most common karyotype, approximately 10% of patients exhibit mosaicism due to mitotic nondisjunction, which may occur in various karyotypic combinations such as 46,XX/47,XXX, 47,XXX/48,XXXX, or 45,X/47,XXX [4].

In this study, we aimed to systematically evaluate the demographic, clinical, and cytogenetic features of patients diagnosed with Triple X syndrome and followed in our department between 2008 and 2025, and to compare our findings with those reported in the literature.

Methods

The patient registry of the Department of Pediatric Genetics at Hacettepe University Faculty of Medicine was retrospectively reviewed to identify cases diagnosed with Triple X syndrome between 2008 and 2025. Patients with a confirmed cytogenetic diagnosis of Triple X syndrome, including both non-mosaic and mosaic karyotypes, were included in the study.

Patients were evaluated with respect to their presenting complaints, indications for chromosomal analysis, and the diagnostic methods used, including conventional karyotype analysis and chromosomal microarray analysis. Cytogenetic data, including karyotype results and the mosaicism status, were retrieved from laboratory records. Demographic data, including age at diagnosis, current age, parental consanguinity, and maternal and paternal ages at the time of birth, were recorded. Prenatal findings, birth characteristics, and anthropometric measurements at birth and at the time of presentation were evaluated. Clinical features, dysmorphic characteristics, neurodevelopmental findings, associated congenital anomalies, endocrine disorders, visual and hearing assessments, and the presence of comorbidities were also assessed.

Conventional G-banded karyotype analysis was performed on peripheral blood lymphocytes for cytogenetic diagnosis and karyotypes were reported in accordance with the International System for Human Cytogenomic Nomenclature (ISCN) [5]. Chromosomal microarray analysis was conducted using the Thermo Fisher Applied Biosystems CytoScan Optima oligonucleotide array (Thermo Fisher Scientific, Waltham, MA, USA), and data were analyzed with Chromosome Analysis Suite (ChAS) software, version 4.4.

Ethical approval for the study was obtained from the Hacettepe University Ethics Committee (SBA 25/906).

Results

A total of 20 patients diagnosed with Triple X syndrome were included in the study; 13 (65%) had a non-mosaic 47,XXX karyotype, while 7 (35%) had mosaic chromosomal constitutions. Among the mosaic cases, five had a 46,XX/47,XXX karyotype, and two had mosaic karyotypes including Turner syndrome cell lines 45,X/47,XXX. All patients underwent chromosomal analysis, with two patients diagnosed by chromosomal microarray analysis followed by karyotyping. One of the patients evaluated by chromosomal microarray analysis had a 47,XXX karyotype, while the other had mosaic 45,X/47,XXX.

Four patients received a prenatal diagnosis, whereas four others were diagnosed in adulthood. One patient was referred during the prenatal period, while the others presented postnatally. The indications for prenatal diagnosis were increased risk on prenatal screening tests and advanced maternal age. The age at initial evaluation ranged from 1 day to 48 years, with a mean age of 10.8 years. Among the 16 patients diagnosed postnatally, the mean age at diagnosis was 11.5 years (range: 1.5 months–48 years). One patient died at 2.5 months of age due to congenital heart disease; the mean current age of the remaining patients was 19.5 years, ranging from 3.2 to 58 years. The mean maternal and paternal ages at delivery were 32.3 and 36.3 years, respectively. Parental consanguinity was present in five families. A history of preterm birth was present in three patients.

One of the patients with Turner syndrome cell lines (45,X/47,XXX) was referred due to critical aortic stenosis with endocardial fibroelastosis, whereas the other presented with short stature. Among the patients diagnosed during childhood, the most common reasons for referral were growth retardation, developmental delay, and dysmorphic features. Among the four women who presented in adulthood, the reasons for

referral included having a child with a chromosomal abnormality, recurrent pregnancy loss, and premature ovarian insufficiency in two patients.

The mean height, weight, and head circumference SDS values at presentation among patients diagnosed during childhood were −1.19, −1.06, and −0.92, respectively. Dysmorphic features were present in 94.1% of patients with available data, and the most common findings are summarized in Table 1. Developmental delay was observed in seven patients, three of whom were born prematurely at 26, 29, and 32 weeks of gestation. Among these preterm patients, one born at 29 weeks was diagnosed with autism and another born at 32 weeks developed seizures; however, their cognitive levels could not be objectively assessed. Among the remaining patients, two had borderline intellectual functioning, one had mild intellectual disability, and one had moderate intellectual disability. Attention-deficit/hyperactivity disorder (ADHD) was identified in two patients, and a history of febrile seizures was noted in one patient. Cranial MRI of one patient with a history of preterm birth revealed extensive areas with encephalomalacia and reduced parenchymal volume. No significant central nervous system abnormalities were observed in the other patients who underwent MRI. Among endocrine disorders, hypothyroidism was identified in four patients and adrenal insufficiency in two patients, with one patient affected by both conditions; premature ovarian failure (POF) was observed in two patients. As additional comorbidities, hypogammaglobulinemia was observed in two patients and a history of hematuria was noted in two patients. The demographic characteristics, anthropometric measurements, and systemic findings of the patients are summarized in Table 1.

Table 1. Demographic, anthropometric, and clinical characteristics of the patients

Characteristic	Value
Demographic characteristics	
Age at referral (years)	Mean 10.8 (range prenatal–48 years)
Age at diagnosis (years)	Mean 11.5 (range prenatal–48 years)
Current age (years)	Mean 19.5 (range 3.2–58)
Maternal age at delivery (years)	Mean 32.3 (range 22–46)
Paternal age at delivery (years)	Mean 36.3 (range 26–53)
Parental consanguinity	5/20 (25%)
Anthropometric measurements	
Birth weight	2.6 kg (range: 955–3,570 g)
Height SDS	−1.19 ± 1.55
Weight SDS	−1.06 ± 1.41
Head circumference SDS	−0.92 ± 1.50
Dysmorphic features	
Epicanthal folds	6/17 (35.3%)
Hypertelorism	4/17 (23.5%)
Upslanting palpebral fissures	2/17 (11.7%)
Clinodactyly	4/17 (23.5%)
Pectus deformity	2/17 (11.7%)
Scoliosis	3/17 (17.6%)
Developmental delay	7/16 (43.7%)
Cognitive impairment	4/7 (57.1%)
Endocrine problems	7/13 (53.8%)
Congenital heart disease	7/13 (53.8%)
Visual problems	3/11 (27.2%)
Hearing loss	3/11 (27.2%)

Discussion

Triple X syndrome is the most prevalent sex chromosome aneuploidy in females. However, it is estimated that only approximately 10% of patients with Triple X syndrome are diagnosed, as most do not present with clearly recognizable dysmorphic features at birth that would prompt clinical suspicion [3,6]. The rate of prenatal diagnosis has increased with the widespread use of non-invasive prenatal testing (NIPT). In our cohort, there were no patients diagnosed through NIPT; however, as NIPT is increasingly adopted in our country, the rate of incidentally diagnosed patients is likely to increase.

In the postnatal period, diagnosis is usually established through chromosome analysis performed for hypotonia, developmental delay, or minor dysmorphic features [3]. In a large cohort study including 74 cases, 44 diagnosed prenatally and 30 postnatally, medical outcomes were shown to be more favorable in the prenatally diagnosed group [4]. However, this difference was suggested to reflect the fact that postnatal diagnoses are typically made based on medical indications such as developmental delay, unlike the largely incidental nature

of prenatal detection. In our cohort, the indications for postnatal chromosome analysis were consistent with the literature; however, among the patients diagnosed prenatally, one showed normal development, one had intellectual disability, one had ADHD, and one with mosaic 46,XX/47,XXX exhibited motor developmental delay.

In Triple X syndrome, the mean maternal age at delivery is reported to be approximately 33 years, and affected newborns tend to have birth weights 400–500 g lower than average, yet they generally present with a normal appearance at birth [2]. In our study, the mean maternal age was found to be similar (32.3 years), but the relatively lower birth weight observed in our cohort was thought to be attributable to patients with a history of premature birth.

In childhood, accelerated linear growth has been reported, with average height typically exceeding the 75th percentile [2]. Although it has been suggested that Triple X syndrome should be considered in the evaluation of females with tall stature, individuals with short stature have also been reported [3,7]. In terms of body proportions, the extremities tend to be relatively long. The mean height SDS in our cohort was −1.19, which is lower than expected. Our cohort may be subject to ascertainment bias, as it primarily included patients referred postnatally due to growth retardation and endocrine disorders, as well as individuals with mosaic karyotypes including 45,X/47,XXX. Therefore, it should be kept in mind that considerable phenotypic variability exists among patients with Triple X syndrome, and tall stature is not a universal feature, particularly in those with mosaic karyotypes including a 45,X cell line.

Clinodactyly and epicanthal folds are the most common minor dysmorphic features reported [2,3]. Although prominent dysmorphic features are not typically expected in affected individuals, other reported findings include hypertelorism, upslanting palpebral fissures, high-arched palate, pes planus, pectus excavatum, kyphoscoliosis, and joint hyperextensibility [3,4]. Although our patients did not exhibit a typical facial gestalt, minor dysmorphic features consistent with those reported in the literature were observed (Table 1).

Congenital anomalies such as cleft lip or palate, cardiac defects, and genitourinary abnormalities may accompany the condition [3,4]. Additional reported features comprise gastrointestinal complaints, including gastroesophageal reflux, constipation, and abdominal pain, as well as neurological symptoms such as seizures, headaches, and tremor, and various ophthalmologic and dental problems [3,4]. The most frequently observed congenital anomaly in our cohort was congenital heart disease.

Sex chromosome aneuploidies are known to be associated with neurodevelopmental problems. In the presence of an additional sex chromosome, such as triple X syndrome, increased rates of autism and social anxiety have been reported; however, when interpreting these elevated risks, ascertainment bias must be taken into account [8]. Moreover, it has been reported that the same aneuploidy can manifest with markedly different phenotypes even within the same family [8]. In affected females, a mean reduction of approximately 20 points in overall intelligence quotient (IQ) has been observed, with both verbal and performance IQ being affected; however, deficits in verbal IQ are significantly more pronounced [7]. In addition, attention deficit, learning difficulties, delayed motor development, speech and language impairments, behavioral problems, and a range of psychiatric disorders, including depression, anxiety, and psychotic disorders, have been reported [7,8]. In line with the literature, several patients in our cohort exhibited neurodevelopmental and neuropsychiatric findings, including developmental delay, intellectual disability, learning disabilities, ADHD, and anxiety; however, only one patient had a diagnosis of epilepsy. Notably, three of the patients with neurodevelopmental impairment had a history of prematurity, and the patient with seizures was also born prematurely.

Auditory processing disorders, which may contribute to delayed language development, have been described in affected patients, whereas hearing loss is not considered a commonly reported feature [2]. In our cohort, hearing loss was identified in three patients. Similarly, although ophthalmological anomalies are not among the typical features associated with the syndrome, case reports have been reported involving ocular pathologies such as high myopia and chorioretinal coloboma [9,10]. In our cohort, two patients had refractive errors, and in one patient with a history of premature birth, absent bilateral responses were observed on visual evoked potentials, while electroretinography revealed bilaterally delayed latency responses.

Although most women with Triple X syndrome exhibit normal reproductive function, an increased frequency

of POF has been reported, and 3.8% of women with POF have been found to have Triple X syndrome [11]. In our cohort, two of the patients who presented in adulthood were referred due to POF; however, this proportion may increase with advancing age. In addition, while hypothyroidism is not considered a common finding among other endocrine problems, autoimmune thyroid disorders have been reported in patients with Triple X syndrome [12]. Adrenal insufficiency has also been reported and was described as coincidentally occurring with congenital adrenal hyperplasia [13]. In our cohort, hypothyroidism was observed in a total of four patients; one patient had Hashimoto thyroiditis, and another patient exhibited central hypothyroidism accompanied by central adrenal insufficiency; however, further molecular investigations to evaluate a hypopituitarism etiology could not be performed. The other patient suspected of having adrenal insufficiency had a mosaic 45,X/47,XXX karyotype and underwent surgery for critical aortic stenosis.

The main limitation of this study is the insufficient sample size of the patient groups, preventing comparative analyses among patients with different chromosomal constitutions.

In conclusion, given that Triple X syndrome is a relatively common chromosomal disorder, it should be considered in patients presenting with congenital anomalies and neurodevelopmental problems in childhood, and particularly in patients with reproductive issues in adulthood. The significant clinical variability observed in our cohort further underscores the importance of considering this condition to prevent delayed diagnosis.

Author contribution

Conception and design: G.Ü.D., G.E.U., P.Ö.Ş.K.; Data acquisition: N.B.A.; Data analysis: G.Ü.D., N.B.A., P.Ö.Ş.K.; Data interpretation: G.Ü.D., N.B.A., P.Ö.Ş.K.; Drafting of the manuscript: G.Ü.D.; Critical revision of the manuscript: G.Ü.D., N.B.A., G.E.U., P.Ö.Ş.K. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Ethics Committee (Date: November 17, 2025, Decision/ Protocol No: SBA 25/906). Ethics committee approval and informed consent were not required for this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study..

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acta medica RESEARCH ARTICLE

Subclinical inflammation, endothelial dysfunction and atrial electrical remodeling in early-onset paroxysmal atrial fibrillation without comorbidities

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Abstract

Objective: Early-onset paroxysmal atrial fibrillation (PAF) in individuals without conventional cardiovascular risk factors has traditionally been labeled as "lone AF." Recent evidence suggests that subtle structural, electrical, and functional abnormalities may still exist. This study evaluated atrial conduction, diastolic function, endothelial function, and systemic inflammation in early-onset PAF patients without structural heart disease or overt comorbidities.

Methods: In this cross-sectional study, 40 patients aged 18–65 years with documented early-onset PAF were compared with 40 age and sex matched healthy individuals in sinus rhythm. All subjects underwent measurement of P wave dispersion and signal-averaged P wave duration, echocardiographic assessment of diastolic parameters, evaluation of endothelial function using flow-mediated dilation (FMD), and analysis of systemic inflammation via high-sensitivity C-reactive protein (hsCRP).

Results: Patients with PAF demonstrated significantly increased P wave dispersion (51.63 ± 11.17 ms vs. 35.13 ± 6.15 ms; $p < 0.001$) and prolonged signal-averaged P wave duration (146.75 ± 19.68 ms vs. 124.40 ± 9.05 ms; $p < 0.001$). Diastolic dysfunction was evident, characterized by a reduced E/A ratio and elevated septal E/E′. Left atrial volume index was significantly higher in the PAF group (29.79 ± 3.94 mL/m^2 vs. 28.23 ± 1.74 mL/m^2; $p = 0.025$). Endothelial function was impaired, as reflected by lower FMD values (5.27 ± 1.94% vs. 6.65 ± 1.78%; $p = 0.001$), while hsCRP levels were significantly higher in the PAF group (0.40 [0.30–0.55] vs. 0.24 [0.20–0.30] mg/dL; $p < 0.001$). Multivariate analysis identified signal-averaged P wave duration, P wave dispersion, mitral E wave velocity, septal E/E′, and left atrial volume index as independent predictors of PAF.

Conclusion: Even in the absence of overt cardiovascular disease, early-onset PAF is associated with meaningful disturbances in atrial conduction, diastolic performance, endothelial function, and systemic inflammation. These findings support the presence of early atrial cardiomyopathy and underscore the need for comprehensive cardiovascular evaluation in younger PAF patients.

Keywords: paroxysmal atrial fibrillation, trial remodeling, inflammation, endothelial dysfunction, diastolic function, signal-averaged ECG

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, affecting approximately 1–2% of the general population, with its prevalence increasing with age [1,2]. AF is associated with significant cardiovascular morbidity and mortality, including ischemic stroke, heart failure, and reduced quality of life, and it often necessitates long-term pharmacological treatment [3,4]. Established risk factors include hypertension, structural heart disease, heart failure, diabetes mellitus, thyroid disorders, and advancing age [3-5].

Historically, the term "lone atrial fibrillation" was used to describe AF in younger individuals (typically under 60 years) without structural heart disease or other identifiable causes [6]. However, recent guidelines discourage the use of this term due to its limited clinical utility and the growing understanding that subclinical factors often contribute to AF development, even in the absence of overt comorbidities [7,8]. Instead, the focus has shifted toward characterizing the clinical and biological profile of patients without traditional risk factors rather than labeling them as having "lone AF" [9].

Contemporary insights into AF pathophysiology highlight a multifactorial etiology involving atrial remodeling, oxidative stress, systemic inflammation, genetic predisposition, and autonomic imbalance [10-12]. These mechanisms promote structural and electrical changes in atrial tissue that facilitate the initiation and maintenance of the arrhythmia.

AF recurrence and progression are strongly associated with atrial remodeling processes, which include structural, electrical, and contractile alterations. Inflammation, endothelial dysfunction, diastolic dysfunction, and heterogeneous atrial conduction may act individually or synergistically to promote this remodeling [10-13].

Although individual studies have evaluated the relationship between paroxysmal AF and inflammation, left ventricular (LV) diastolic function, endothelial function, and intra-/inter-atrial conduction times, there is a lack of comprehensive research that investigates these parameters collectively and assesses their interplay.

The aim of this study is to investigate the roles of inflammation, endothelial function, intra- and inter-atrial conduction properties, and diastolic function in patients with paroxysmal AF without overt structural heart disease, compare these parameters with age- and sex-matched controls in sinus rhythm, and explore their interrelations.

Methods

Study population

This cross-sectional study included 40 patients aged 18 to 65 years who presented with palpitations to the Hacettepe University Faculty of Medicine, Department of Cardiology, and were diagnosed with paroxysmal atrial fibrillation (PAF) documented by 24-hour Holter monitoring (minimum AF episode duration: ≥30 seconds). Only patients without identifiable structural heart disease, hypertension, or systemic comorbidities were included, representing a cohort with early-onset AF of unknown etiology. A control group of 40 age- and sex-matched healthy individuals with no history of arrhythmia or systemic disease was also enrolled.

Detailed clinical histories were taken. Participants with suspected obstructive sleep apnea (based on structured patient and family interviews), a family history of AF, or any clinical or subclinical cardiovascular or systemic condition were excluded. Demographic data, anthropometric measurements, physical examinations, and baseline laboratory tests were collected.

Exclusion criteria included: any structural heart disease, coronary artery disease, cardiomyopathy, moderate-to-severe valvular disease, thyroid dysfunction, pulmonary disease, hypertension, diabetes mellitus, liver or renal dysfunction, autoimmune or connective tissue disorders, active or chronic inflammatory conditions, malignancy, regular medication use (including anti-inflammatory or antiarrhythmic drugs), and smoking.

Data collection and measurements

Electrocardiographic evaluation

Standard 12-lead surface ECG and signal-averaged ECG (SAECG) recordings were obtained using the General

Electric MAC 5000 system while subjects were in sinus rhythm. After 15 minutes of rest in the supine position, P wave durations were measured. P wave onset was defined as the first deflection from the isoelectric line, and offset as the return to baseline. Leads with unclear P wave morphology were excluded, and measurements from at least 10 analyzable leads were required to ensure reliability. All included participants met this criterion, and no subjects were excluded due to insufficient ECG lead quality.

P wave durations were averaged from three consecutive beats. P maximum (Pmax), P minimum (Pmin), and P wave dispersion (Pd = Pmax − Pmin) were calculated. All ECG measurements were independently assessed by two observers, with intra- and inter-observer variability for Pmax and Pd being <5%.

SAECG P wave durations were derived from orthogonal leads after filtering (band-pass 40–250 Hz; 50 Hz notch filter). A composite signal of 250–350 beats was averaged to reduce noise, and duration was measured using a vector magnitude algorithm.

Transthoracic echocardiography (TTE)

TTE was performed using a 2.5 MHz transducer (GE Vingmed System Six) during sinus rhythm in the left lateral decubitus position. Standard parasternal and apical views were acquired. Measurements included left atrial (LA) diameter, left ventricular (LV) dimensions, wall thickness, and ejection fraction. LA volume was indexed to body surface area (LAVI). Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [14].

LV diastolic function was evaluated via pulsed-wave Doppler at the mitral inflow tract, measuring early (E) and late (A) diastolic velocities, E/A ratio, deceleration time (DT), and isovolumetric relaxation time (IVRT). At least three beats at end-expiration were averaged.

Color M-mode Doppler was used to assess mitral inflow propagation velocity (Vp). The slope of early diastolic flow was measured from the mitral valve annulus apically.

Tissue doppler imaging (TDI)

TDI was performed in the apical four-chamber view. Early (E'), late (A'), and systolic (S) myocardial velocities were recorded at the septal and lateral mitral annulus.

Inflammatory marker: High-sensitivity c-reactive protein (hsCRP)

Serum hsCRP was measured via nephelometry using the IMMAGE High Sensitivity CRP Kit (Beckman Coulter) in the central biochemistry laboratory.

Assessment of endothelial function: Flow-mediated dilation (FMD)

Endothelial function was evaluated by measuring brachial artery flow-mediated dilation (FMD) following guidelines from the International Brachial Artery Reactivity Task Force. Participants fasted for 8–12 hours and avoided caffeine and alcohol for 12 hours prior to the test. A 10 MHz linear array transducer was used.

After measuring baseline brachial artery diameter, a forearm cuff was inflated 50 mmHg above systolic pressure for 5 minutes and then deflated. Arterial diameter was re-measured 60 seconds after deflation. FMD was calculated as:

FMD (%) = [(post-hyperemia diameter − baseline diameter) / baseline diameter] × 100

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Hacettepe University Ethics Committee (Approval No: LUT 12/44 – 30), and the research was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software, Version 11.4.2 (MedCalc Software Ltd., Ostend, Belgium). The normality of distributions was assessed with the Kolmogorov–Smirnov test. Continuous variables were expressed as

mean ± SD or median (IQR), and categorical variables as counts and percentages.

Independent samples t-test or Mann–Whitney U test was used for comparing continuous variables, and Chi-square or Fisher's exact test for categorical variables. Variables associated with AF status were first analyzed using univariate logistic regression. Significant variables were included in a multivariate logistic regression model. ROC curve analyses were performed for parameters such as Pd, SAECG P wave duration, LAVI, E/E' septal, and E velocity. Correlations were examined using Pearson or Spearman coefficients as appropriate. A p-value < 0.05 was considered statistically significant.

Results

A total of 80 participants were enrolled in the study, including 40 patients with early-onset paroxysmal atrial fibrillation without identifiable comorbidities and 40 age- and sex-matched healthy controls. There were no significant differences between the two groups in terms of age (47.68 ± 8.47 vs. 48.95 ± 7.09 years; p = 0.468), sex distribution (p = 0.104), or body mass index (BMI; p = 0.180) (Table 1).

Transthoracic echocardiographic assessment demonstrated significantly larger left atrial dimensions in the PAF group. Left atrial diameter was significantly increased in patients with PAF compared to controls (3.50 ± 0.33 cm vs. 3.31 ± 0.38 cm; p = 0.018). Left atrial volume (LAV) (54.8 ± 7.3 mL vs. 50.5 ± 6.8 mL; p = 0.007) and left atrial volume index (LAVI) (29.79 ± 3.94 mL/m^2 vs. 28.23 ± 1.74 mL/m^2; p = 0.025) were also significantly higher in the PAF group (Table 2). Left ventricular ejection fraction and other systolic parameters were similar between groups.

Assessment of diastolic function revealed impaired left ventricular filling in the PAF group. Peak E wave velocity was significantly lower in patients with PAF compared with controls (69 [60–78] cm/s vs. 85 [74–96] cm/s; p = 0.040), along with a reduced E/A ratio (1.0 ± 0.22 vs. 1.15 ± 0.31; p = 0.019). Deceleration time (DT) (238.55 ± 50.11 ms vs. 218.45 ± 34.4 ms; p = 0.040) and isovolumetric relaxation time (IVRT) (115.00 ± 28.84 ms vs. 99.28 ± 14.37 ms; p = 0.033) were significantly prolonged in the PAF group (Table 3).

Table 1. Baseline characteristics of the study population

Variables	PAF (n = 40)	Control (n = 40)	P Value
Age (years)	47.68 ± 8.47	48.95 ± 7.09	0.468
Gender (Female)	22 (55.0%)	29 (72.5%)	0.104
Systolic Blood Pressure (mmHg)	123.75 ± 7.32	125 ± 7.34	0.504
Diastolic Blood Pressure (mmHg)	80.3 ± 6.09	80.5 ± 5.97	0.893
Heart Rate (beats/min)	76.03 ± 13.19	75.95 ± 7.66	0.975
Body Mass Index (BMI, kg/m^2)	26.76 ± 2.25	27.45 ± 2.28	0.180
Body Surface Area (BSA, m^2)	1.84 ± 0.18	1.79 ± 0.18	0.124
Total Cholesterol (mg/dL)	185.88 ± 27.40	187.95 ± 25.70	0.728
Triglycerides (mg/dL)	113.50 (100-130)	125.5 (110-140)	0.273
LDL (mg/dL)	110.38 ± 20.29	115.58 ± 19.19	0.242
HDL (mg/dL)	51.5 (48-55)	52.5 (49-56)	0.567
Glucose (mg/dL)	87.83 ± 11.03	91.65 ± 8.17	0.082
Urea (mg/dL)	14.62 ± 3.85	14.18 ± 5.44	0.672
Creatinine (mg/dL)	0.80 ± 0.13	0.74 ± 0.14	0.057
ALT (U/L)	20.5 (18-25)	23 (20-28)	0.086
AST (U/L)	19.96 ± 4.63	21.33 ± 3.33	0.133

Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Table 2. Baseline echocardiographic findings

Variables	PAF (n = 40)	Control (n = 40)	P Value
LVEDD (cm)	4.66 ± 0.38	4.62 ± 0.31	0.653
LVESD (cm)	2.99 ± 0.33	2.86 ± 0.31	0.063
EF (%)	65 (62-68)	66 (63-69)	0.086
FS (%)	35 (33-37)	36 (34-38)	0.090
IVS (cm)	1.00 (0.95-1.05)	0.91 (0.87-0.95)	0.096
PW (cm)	1.00 (0.95-1.05)	0.90 (0.86-0.94)	0.148
LA Diameter (cm)	3.50 ± 0.33	3.31 ± 0.38	0.018
LA Volume (mL)	54.8 ± 7.3	50.5 ± 6.7	0.007
LAVI (mL/m^2)	29.79 ± 3.94	28.23 ± 1.74	0.025
LVM (g)	176.38 ± 27.17	167.88 ± 30.78	0.194
LVMI (g/m^2)	95.81 ± 14.25	94.43 ± 16.72	0.692
sPAP (mmHg)	22.68 ± 4.33	23.13 ± 4.19	0.638

EF: Ejection Fraction, FS: Fractional Shortening, IVS: Interventricular Septum, PW: Posterior Wall (Thickness) LA: Left Atrium, LAV: Left Atrial Volume, LAVI: Left Atrial Volume Index, LVEDD: Left Ventricular End-Diastolic Diameter, LVESD: Left Ventricular End-Systolic Diameter, LVM: Left Ventricular Mass, LVMI: Left Ventricular Mass Index, sPAP: Systolic Pulmonary Artery Pressure
Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Table 3. Diastolic function parameters

Variables	PAF (n = 40)	Control (n = 40)	P Value
Peak E wave velocity (cm/s)	69 (60-78)	85 (74-96)	0.040
Peak A wave velocity (cm/s)	68.5 (60-77)	67.5 (58-77)	0.528
E/A ratio	1.00 ± 0.22	1.15 ± 0.31	0.019
DT (ms)	238.55 ± 50.11	218.45 ± 34.40	0.040
IVRT (ms)	115.00 ± 28.84	99.28 ± 14.37	0.033
Vp (cm/s)	57 ± 16	59 ± 10	0.451
E/Vp ratio	1.31 (1.20-1.42)	1.44 (1.33-1.55)	0.408
Lateral E′ (cm/s)	10.47 ± 3.61	13.94 ± 1.91	0.001
Lateral A′ (cm/s)	9.65 ± 1.82	10.70 ± 2.71	0.045
Lateral S (cm/s)	6.82 (6.3-7.3)	7.20 (6.7-7.7)	0.832
Lateral E′/A′ ratio	1.13 ± 0.44	1.38 ± 0.40	0.009
Septal E′ (cm/s)	8.90 ± 2.25	12.73 ± 1.69	0.001
Septal A′ (cm/s)	8.99 ± 1.84	10.13 ± 2.97	0.042
Septal S (cm/s)	6.90 ± 1.23	7.39 ± 1.63	0.131
Septal E′/A′ ratio	1.04 ± 0.37	1.37 ± 0.44	0.001
E/Septal E′	8.11 ± 1.74	6.38 ± 1.85	0.001
E/Lateral E′	7.08 ± 1.70	5.82 ± 1.73	0.002
Average E′ (cm/s)	9.68 ± 2.73	13.33 ± 1.26	0.001
E/Average E′	7.47 ± 1.48	6.03 ± 1.64	0.001

DT: Deceleration Time, IVRT: Isovolumetric Relaxation Time, Vp: Mitral Flow Propagation Velocity
Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Tissue Doppler imaging demonstrated significantly lower septal and lateral E′ velocities in the PAF group (septal E′: 8.90 ± 2.25 cm/s vs. 12.73 ± 1.69 cm/s; p = 0.001; lateral E′: 10.47 ± 3.61 cm/s vs. 13.94 ± 1.91 cm/s; p = 0.001). Accordingly, septal and average E/E′ ratios were significantly higher in patients with PAF (septal E/E′: 8.11 ± 1.74 vs. 6.38 ± 1.85; p = 0.001; average E/E′: 7.47 ± 1.48 vs. 6.03± 1.64; p = 0.001) (Table 3).

Electrocardiographic analysis revealed significantly prolonged atrial conduction parameters in the PAF group. P wave dispersion was markedly increased in patients with PAF (51.63 ± 11.17 ms vs. 35.13 ± 6.15 ms; p = 0.001). Signal-averaged ECG P wave duration was also significantly longer in the PAF group (146.75 ± 19.68 ms vs. 124.40 ± 9.05 ms; p = 0.001), as was maximum P wave duration (Pmax) (112.13 ± 16.68 ms vs. 98.00 ± 7.75 ms; p = 0.001) (Table 4).

Endothelial function assessed by flow-mediated dilation was significantly impaired in the PAF group (5.27 ± 1.94% vs. 6.65 ± 1.78%; p = 0.001), whereas baseline brachial artery diameters did not differ between groups (Table 5).

Inflammatory status, as reflected by high-sensitivity C-reactive protein (hsCRP), was significantly elevated in patients with PAF (median 0.40 mg/dL [0.30–0.55] vs. 0.24 mg/dL [0.20–0.30]; p = 0.001). P wave dispersion showed a strong positive correlation with hsCRP levels (r = 0.810; p = 0.001), while signal-averaged ECG P wave duration was moderately correlated with hsCRP (r = 0.364; p = 0.001). P wave dispersion and P wave duration were also moderately correlated with each other (r = 0.613; p = 0.001). Septal E/E′ ratio demonstrated significant positive correlations with both P wave dispersion (r = 0.317; p = 0.004) and P wave duration (r = 0.269; p = 0.016) (Figure 1).

Flow-mediated dilation was inversely correlated with LAVI (r = –0.245; p = 0.028), hsCRP (r = –0.401; p < 0.001), P wave dispersion (r = –0.400; p = 0.001), and P wave duration (r = –0.230; p = 0.040). LAVI showed weak but significant correlations with both P wave dispersion (r = 0.295; p = 0.009) and septal E/E′ ratio (r = 0.221; p = 0.049).

Univariate logistic regression analysis identified several parameters significantly associated with the presence of early-onset PAF, including left atrial dimensions, diastolic function indices, electrocardiographic markers of atrial conduction, hsCRP, and FMD (Table 6). In multivariate logistic regression analysis, signal-averaged ECG P wave duration (OR = 1.161; 95% CI: 1.01–1.34; p = 0.040), P wave dispersion (OR = 1.322; 95% CI: 1.01–1.75; p = 0.045), septal E/E′ ratio (OR = 21.121; 95% CI: 1.90–234.40; p = 0.013), mitral E wave velocity (OR = 0.76; 95% CI: 0.61–0.94; p = 0.012), and LAVI (OR = 1.964; 95% CI: 1.16–3.18; p = 0.038) emerged as independent predictors of early-onset PAF without comorbidities (Table 7).

Table 4. P wave analysis data from 12-lead surface ECG and signal-averaged ECG

Variables	PAF (n = 40)	Control (n = 40)	P Value
Pmax (ms)	112.13 ± 16.68	98.00 ± 7.75	0.001
Pmin (ms)	60.5 ± 14.31	62.88 ± 6.59	0.345
Pd (ms)	51.63 ± 11.17	35.13 ± 6.15	0.001
SAECG P wave duration (ms)	146.75 ± 19.68	124.40 ± 9.05	0.001

SAECG: Signal averaged ECG

Table 5. Baseline brachial artery diameters and flow-mediated dilation values of the groups

Variables	PAF (n = 40)	Control (n = 40)	P Value
FMD (%)	5.27 ± 1.94	6.65 ± 1.78	0.001
Baseline brachial artery diameter (cm)	3.89 (3.7-4.1)	3.74 (3.55-3.95)	0.182

FMD: Flow-Mediated Dilation
Variables are presented as mean ± SD or median (IQR) according to distribution assessed by the Kolmogorov–Smirnov test.

Receiver operating characteristic curve analyses demonstrated strong discriminatory performance for several parameters. P wave dispersion yielded an area under the curve (AUC) of 0.906 ($p < 0.001$), while signal-averaged ECG P wave duration showed an AUC of 0.857 ($p < 0.001$). Optimal cut-off values, along with sensitivity and specificity, are presented in Figure 2 and Figure 3.

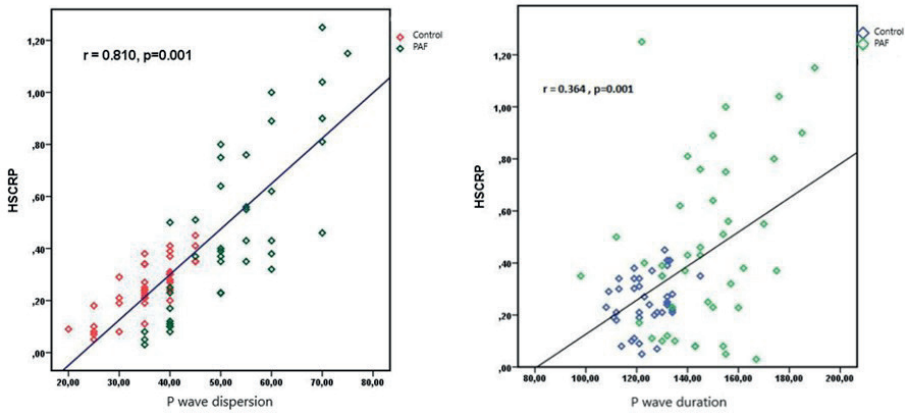

Figure 1. Correlation of hsCRP levels with P wave duration and P wave dispersion. The figure illustrates significant positive correlations between hsCRP levels and both P wave duration and P wave dispersion.

Table 6. Univariate logistic regression analysis of risk factors for PAF

Variables	OR	P Value	95% Confidence Interval(CI)
LA diameter	4.748	0.023	1.245 – 18.112
LAV	1.093	0.010	1.021 – 1.169
LAVI	1.206	0.032	1.016 – 1.406
Peak E wave velocity	0.975	0.038	0.951 – 0.998
E/A ratio	0.129	0.022	0.022 – 0.749
DT	1.011	0.045	1.008 – 1.022
IVRT	1.035	0.007	1.009 – 1.060
Lateral E′	0.662	0.001	0.543 – 0.807
Septal E′	0.377	0.001	0.245 – 0.578
E/Septal E′	1.764	0.001	1.285 – 2.422
E/Lateral E′	1.550	0.003	1.157 – 2.077
E/Average E′	1.837	0.001	1.302 – 2.593
Pmax	1.094	0.001	1.044 – 1.147
SAECG P wave duration	1.115	0.001	1.061 – 1.173
Pd	1.316	0.001	1.157 – 1.497
FMD (%)	0.644	0.004	0.477 – 0.871
hsCRP	101.7	0.001	6.166 – 1679.21

Table 7. Multivariate logistic regression analysis of risk factors affecting PAF

Variables	OR	P Value	95% Confidence Interval (CI)
SAECG P wave duration	1.161	0.040	1.01 – 1.34
Pd	1.322	0.045	1.01 – 1.75
E/E' (septal)	21.121	0.013	1.90 – 234.40
Peak E wave velocity	0.76	0.012	0.61 – 0.94
LAVI	1.964	0.038	1.16 – 3.18

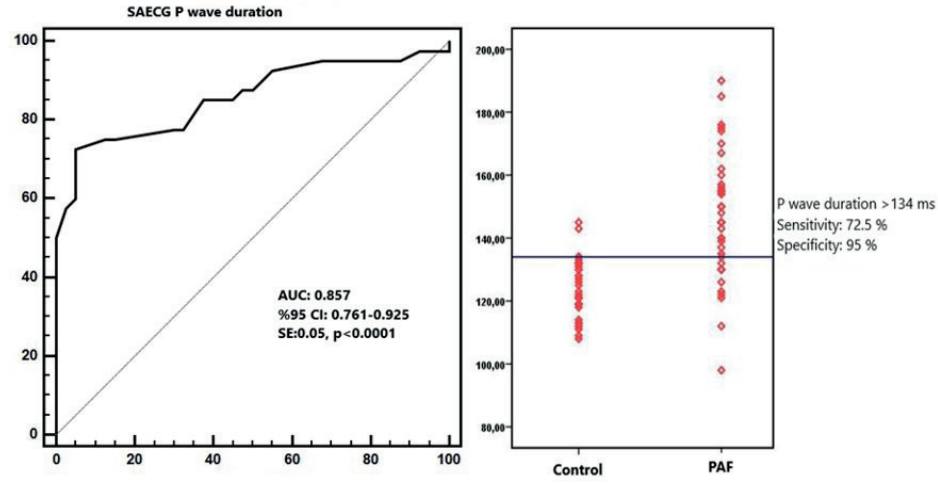

Figure 2. ROC analysis and cut-off value of SAECG P wave duration for predicting the development of PAF

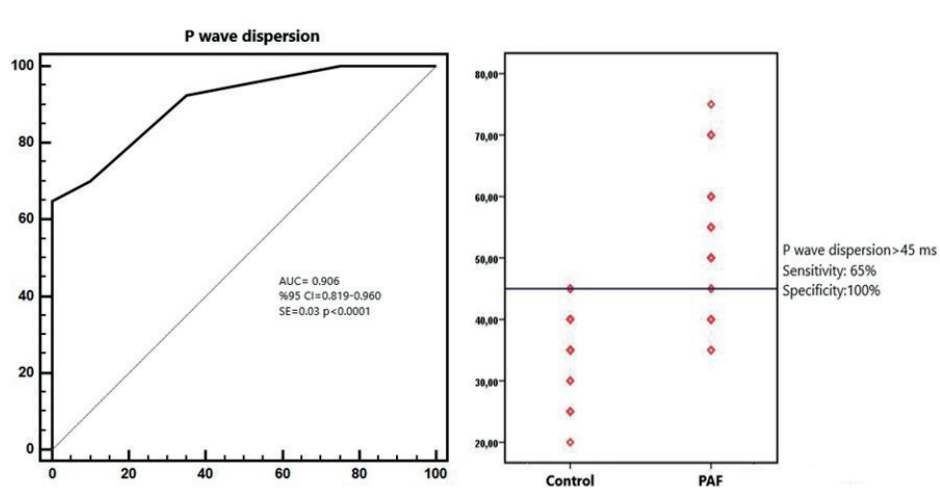

Figure 3. ROC analysis and cut-off value of P wave dispersion for predicting the development of PAF

Discussion

In this study, we investigated atrial conduction properties, left ventricular diastolic function, endothelial function, and systemic inflammation in patients with early-onset PAF without overt structural heart disease or traditional comorbidities. Our findings reveal that even in the absence of identifiable cardiovascular risk factors, PAF is associated with significant alterations in atrial electrophysiology, subclinical diastolic dysfunction, impaired endothelial function, and elevated inflammatory markers.

Patients with PAF exhibited increased P wave dispersion and prolonged signal-averaged P wave duration markers of intra and inter-atrial conduction heterogeneity that reflect early atrial electrical remodeling. These conduction abnormalities were significantly correlated with elevated hsCRP levels, supporting the role of inflammation in AF pathogenesis. Inflammatory cytokines can promote atrial fibrosis and conduction slowing through the activation of profibrotic pathways (e.g., TGF-β) and inflammasome-mediated myocyte injury [15,16]. Recent mechanistic studies confirm that NLRP3 inflammasome activation contributes to atrial electrical instability, while targeted inhibition of inflammasome signaling reduces AF vulnerability [17,18].

Interestingly, recent studies evaluating atrial electromechanical conduction and left atrial functional properties in patients undergoing interventions for atrial fibrillation have demonstrated that even in the absence of overt comorbidities, subtle atrial remodeling and functional impairment can be detected [19,20]. Although these studies primarily focused on echocardiographic and mechanical parameters rather than surface ECG indices, their findings complement our results by supporting the presence of early atrial remodeling in apparently healthy individuals with AF. Together, these observations reinforce the concept that atrial electrical abnormalities identified in our study coexist with subclinical structural and functional changes of the left atrium.

We also observed impaired left ventricular diastolic function in the PAF group, evidenced by reduced E wave, lower E/A ratios, prolonged deceleration time and isovolumetric relaxation time, and elevated E/E′ ratios. These findings suggest increased left atrial pressure and wall stress, which can lead to atrial dilation and fibrosis—mechanical contributors to AF onset and maintenance [21,22]. Notably, the strong correlations between E/E′ and both conduction parameters and hsCRP underscore the interplay between mechanical dysfunction, electrical instability, and systemic inflammation.

Endothelial function, as measured by FMD, was significantly reduced in the PAF group. FMD showed inverse correlations with LAVI, hsCRP, and conduction parameters, indicating that endothelial dysfunction may not only reflect systemic vascular pathology but also actively contribute to AF pathogenesis. Impaired nitric oxide bioavailability, increased oxidative stress, and altered vascular tone in endothelial dysfunction may augment systemic inflammation and atrial remodeling [23,24]. Furthermore, recent studies suggest that microvascular ischemia of the atrial myocardium, even in the absence of epicardial coronary artery disease, may promote low-grade fibrosis and create a vulnerable substrate for AF [25]. Emerging evidence also suggests that endothelial senescence may exacerbate inflammation and structural remodeling in AF-prone atria [26].

Additionally, the HALP score has been evaluated as a predictor of AF recurrence after ablation, showing that hematologic and inflammatory parameters can reflect underlying atrial vulnerability [27]. This aligns with our findings where elevated hsCRP correlated with conduction heterogeneity, suggesting that systemic inflammatory status may contribute to early atrial remodeling even in young, low-risk patients.

These results align with emerging data suggesting that patients formerly described as having “lone AF” may, in fact, exhibit early signs of atrial cardiomyopathy. Advanced imaging techniques such as speckle-tracking echocardiography and cardiac MRI have revealed atrial fibrosis, mechanical dysfunction, and reduced strain in AF patients without overt comorbidities [28,29]. The elevated LAVI and diastolic abnormalities in our study support the presence of subtle structural remodeling in this ostensibly healthy population.

Genetic predisposition is another key consideration. Recent genome-wide association studies (GWAS) have identified common variants in ion channel and transcription factor genes associated with AF, particularly in early-onset cases. These variants may predispose to conduction abnormalities and increased

atrial susceptibility to inflammatory or hemodynamic stressors [30]. Thus, the conduction changes observed in our patients may reflect a genetically determined atrial substrate. Recent Mendelian randomization studies have also linked genetically predicted IL-6 receptor signaling and CD40 ligand activity with increased AF risk, suggesting an inherited inflammatory susceptibility [31].

Additionally, heightened autonomic nervous system (ANS) activity especially increased vagal tone has been implicated in triggering paroxysmal AF in structurally normal hearts. In young individuals, autonomic imbalance may play a critical initiating role in arrhythmogenesis and influence AF patterns, particularly in the absence of other comorbidities [32].

Importantly, inflammation represents a potentially modifiable contributor to AF. Anti-inflammatory strategies, including colchicine and interleukin-1 antagonists, have demonstrated efficacy in reducing AF recurrence post-cardiac surgery and catheter ablation [33,34]. Given the strong association between hsCRP and conduction indices in our study, targeting inflammatory pathways may hold promise for early intervention in patients with subclinical atrial remodeling. Novel approaches targeting macrophage activity and osteopontin signaling have shown promising anti-fibrotic effects in experimental AF models [35]. Novel inflammatory markers such as interleukin-6, galectin-3, and soluble ST2 are being evaluated as potential biomarkers and therapeutic targets for atrial cardiomyopathy [36].

Although participants were selected to exclude known risk factors, subclinical contributors such as undiagnosed sleep apnea, visceral adiposity, alcohol consumption, or sedentary lifestyle may still influence atrial structure and electrophysiology. Future studies incorporating detailed lifestyle assessments and wearable monitoring could help capture these subtle influences [37]. Environmental triggers such as air pollution and heat exposure have also been identified as transient risk factors for AF events, even in young or low-risk populations [38].

Limitations

This study has several limitations. Its cross-sectional design precludes causal inference. The modest sample size may limit generalizability, and unmeasured confounders such as undiagnosed sleep-disordered breathing, masked hypertension, or lifestyle factors could have influenced the results. Additionally, we assessed inflammation using hsCRP alone, which, while widely validated, does not capture the full complexity of inflammatory signaling. Advanced imaging and genetic testing were not available to further characterize atrial structure or predisposition.

Conclusion

In summary, early-onset PAF in individuals without traditional cardiovascular risk factors is associated with a distinct pathophysiological profile that includes subclinical diastolic dysfunction, systemic inflammation, atrial electrical heterogeneity, and endothelial dysfunction. These findings reinforce the concept of early atrial cardiomyopathy and highlight potential targets for risk stratification and early therapeutic intervention. Future prospective studies should assess whether targeting inflammation and mechanical dysfunction can delay AF progression or improve long-term outcomes in this population.

Author contributions

Conception and design: A.Ü.K., K.A.; Data acquisition: A.Ü.K., T.K., A.B.; Data analysis: A.Ü.K.; Data interpretation: A.Ü.K., T.K., A.B.; Drafting of the manuscript: A.Ü.K., T.K., A.B.; Critical revision of the manuscript: K.A. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Ethical Commitee (Date: June 5, 2012, Decision/ Protocol No: LUT 12/44-30). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors declare that this study received no funding.

Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

Single-center real-world data on the efficacy, safety, and current availability of pegylated interferon-α in hematologic neoplasms

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Abstract

Aims: Pegylated interferon-α (PEG-IFN-α) offers improved pharmacokinetics compared with conventional interferon-α (IFN-α), yet real-world data on its clinical activity and safety across heterogeneous hematologic neoplasms are limited. This study aimed to evaluate the real-world efficacy, durability of response, and toxicity of PEG-IFN-α in patients with diverse hematologic neoplasms.

Methods: This retrospective study evaluated the efficacy, duration of response, and toxicity of PEG-IFN-α using patient medical records and hospital electronic registries. Thirty patients were included: polycythemia vera (PV, n=12), essential thrombocytosis (ET, n=6), chronic myeloid leukemia (n=2), primary myelofibrosis (n=1), systemic mastocytosis (SM,n=3), hypereosinophilic syndrome (HES, n=1), Erdheim–Chester disease (ECD, n=4), and lymphomatoid granulomatosis (LYG, n=1).

Results: PEG-IFN-α was initiated due to resistance to prior therapies in 12 patients (40%), intolerance or toxicity in 10 patients (33.3%), and as first-line treatment in 8 patients (26.7%). Among PV patients, a complete response was achieved in 41.6% and a partial response in 50%. In ET patients, 83.3% achieved a complete response, while 16.7% showed no response. All patients with SM demonstrated clinical improvement when PEG-IFN-α was used as first-line therapy. In ECD patients, follow-up PET imaging showed stable disease in two patients, partial response in one, and no response in one. Partial responses were also observed in patients with HES and LYG. Treatment-related toxicity occurred in 8 patients (26.6%) and led to treatment discontinuation in 6 patients (20%) (including cytopenias, influenza-like symptoms, and elevated liver enzymes).

Conclusion: In this real-world cohort, PEG-IFN-α showed encouraging activity across several hematologic neoplasms, with toxicity and discontinuation rates in line with previously published series of conventional interferon-α; however, its clinical use remains limited by regulatory and access constraints.

Keywords: pegylated interferon-α, myeloproliferative disorders, Erdheim–Chester disease, lymphomatoid granulomatosis

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Introduction

Interferon-α (IFN-α) is an immunomodulatory agent with well-established antitumor activity and a long history of use across a broad spectrum of hematologic neoplasms. By targeting abnormal hematopoietic clones, IFN-α has demonstrated clinical efficacy in disorders including chronic myeloid leukemia (CML), classical myeloproliferative neoplasms, systemic mastocytosis (SM), hypereosinophilic syndrome (HES), selected histiocytic disorders, and rare lymphoproliferative diseases. However, the widespread clinical use of conventional IFN-α has been limited by its unfavorable toxicity profile and inconvenient dosing schedules, resulting in substantial treatment discontinuation.

Pegylated interferon-α (PEG-IFN-α), developed through covalent conjugation with polyethylene glycol, exhibits improved pharmacokinetic properties, including a prolonged serum half-life, reduced clearance, and more stable drug exposure, thereby enabling once-weekly administration and improved tolerability. In chronic-phase CML, prospective trials have primarily explored PEG-IFN-α in combination with tyrosine kinase inhibitors (TKIs), with several randomized, phase III studies demonstrating deeper molecular responses than TKI monotherapy in selected patient populations [1].

Beyond CML, PEG-IFN-α has an established evidence base in classical myeloproliferative neoplasms — particularly polycythemia vera (PV) and essential thrombocytosis (ET)—where prospective studies and long-term follow-up cohorts have reported durable hematologic control and, in some series, molecular responses [2]. In contrast, evidence supporting PEG-IFN-α in non-myeloproliferative hematologic neoplasms and rare entities remains fragmented, largely derived from small observational cohorts or disease-specific case series. In SM, interferon-based therapy has historically served as a cytoreductive option, although its role has diminished with the advent of KIT-targeted agents [3]. Similarly, IFN-α demonstrated early clinical activity in Erdheim–Chester disease (ECD), but contemporary management increasingly favors molecularly targeted therapies when actionable alterations are present [4,5]. In lymphomatoid granulomatosis (LYG), IFN-α has been used as an immunomodulatory approach in selected patients, although data on PEG-IFN-α remain limited [6,7].

In this context, real-world data addressing treatment indications, response patterns, tolerability, and discontinuation rates of PEG-IFN-α across heterogeneous and rare hematologic conditions are particularly informative. Moreover, the evolving regulatory landscape has created a paradox in which interferon-based therapies with long-standing biological and clinical activity may face restricted accessibility in routine practice, while closely related formulations receive indication-specific approvals. This discrepancy further underscores the importance of real-world evidence beyond formal licensing frameworks.

Therefore, this study aimed to evaluate real-world treatment indications, clinical responses, toxicity profiles, and discontinuation rates of PEG-IFN-α in a heterogeneous cohort of patients with hematologic neoplasms and rare entities treated at a tertiary hematology center, and to contextualize these findings within the existing literature, particularly beyond classical myeloproliferative neoplasms.

METHODS

Patients and Methods

Study Design and Patient Selection

This retrospective, single-center study was conducted at Hacettepe University Faculty of Medicine, Department of Hematology. Patients with a diagnosis of hematologic neoplasia who received PEG-IFN-α between January 2014 and August 2016 were identified by screening institutional drug approval records. At the time of treatment, PEG-IFN-α had no established reimbursement indication for hematologic neoplasms in the Turkish Social Security Institution Health Implementation Notification (SUT). Therefore, all patients included in this study received PEG-IFN-α via individual off-label drug-use approvals obtained in accordance with national reimbursement regulations and institutional authorization procedures.

Only patients who had received formal institutional approval and were followed at our center were included in the analysis. Clinical and diagnostic data were obtained from the hospital electronic medical record system and patient files.

Data Collection

The following data were recorded: demographic characteristics, date of diagnosis, previous treatments and treatment responses, indication for initiation of PEG-IFN-α, treatment start date and duration, response to PEG-IFN-α, occurrence of treatment-related toxicity, last follow-up date, and survival status when applicable.

Response and Toxicity Assessment

Treatment responses were evaluated using disease-specific standardized criteria:

European LeukemiaNet (ELN) criteria for CML [8]

International Working Group–Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria for PV and ET [9]

European Myelofibrosis Network (EUMNET) criteria for primary myelofibrosis [10]

Nordic proposal criteria for hypereosinophilic syndrome [11]

Modified consensus criteria for systemic mastocytosis [12]

Cheson criteria for lymphomatoid granulomatosis [13]

Positron emission tomography (PET) imaging for response assessment in ECD [14]

Treatment-related adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [15].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Chicago, IL, USA). Given the retrospective and descriptive nature of the study and the limited sample size, analyses were primarily descriptive. Categorical variables were summarized as counts and percentages, whereas continuous variables were reported as median and range. No formal hypothesis testing or inferential statistical comparisons were conducted.

RESULTS

Patient Characteristics

A total of 30 patients were included (female/male: 17/13), and the median age at treatment initiation was 48 years (range, 23–73). Comorbid conditions were present in 70% of patients (n=21), most commonly hypertension (33.3%, n=10) and a history of thrombosis (33.3%, n=10). At the last follow-up assessment, 86.7% of the cohort (n=26) were alive.

The diagnostic distribution included polycythemia vera (PV, n=12), essential thrombocytosis (ET, n=6), chronic myeloid leukemia (CML, n=2), primary myelofibrosis (PMF, n=1), systemic mastocytosis (SM, n=3), hypereosinophilic syndrome (HES, n=1), Erdheim–Chester disease (ECD, n=4), and lymphomatoid granulomatosis (LYG, n=1).

A prior history of arterial or venous thrombosis was documented in 33.3% of patients (n=10). No arterial or venous thrombotic events occurred during PEG-IFN-α treatment.

Treatment Indications

Overall, PEG-IFN-α was initiated due to resistance to previous therapies in 40% of patients (n=12) and due to intolerance or toxicity related to prior treatments in 33.3% (n=10). In the remaining 26.7% of patients (n=8), PEG-IFN-α was administered as first-line therapy.

All patients with PV, ET, CML, and PMF had previously received standard treatments and were switched to PEG-IFN-α due to treatment resistance or intolerance.

Treatment Response in Classical Myeloproliferative Neoplasms

Among patients with PV, the best response to PEG-IFN-α was complete response in 41.7% (n=5), partial response in 50% (n=6), and no response in 8.3% (n=1). The median time to best response was 4.1 months (range, 0.5–21). None of the PV patients required phlebotomy during treatment. Treatment discontinuation due to toxicity occurred in 50% of PV patients (n=6).

In ET patients, complete response was achieved in 83.3% (n=5), while 16.7% (n=1) showed no response. The median time to best response was 7.3 months (range, 5.1–12.8). No major bleeding or thrombotic events were observed during treatment. Mean platelet counts decreased from 1174.2×10^9/L at baseline to 428.5×10^9/L at 6 months and 405.3×10^9/L at 12 months.

In the two patients with CML, PEG-IFN-α was administered in combination with tyrosine kinase inhibitors due to suboptimal response. One patient achieved a major molecular response, while the other achieved a hematologic response.

The single patient with PMF achieved a partial response, with a median time to best response of 8.1 months.

Baseline patient characteristics, treatment details, response outcomes, and toxicity profiles for patients with PV, ET, CML, and SM are summarized in Table 1.

Treatment Response in Rare Hematologic and Histiocytic Disorders

All three patients with systemic mastocytosis received PEG-IFN-α as first-line therapy and demonstrated clinical improvement. Symptom relief, particularly resolution of pruritus and skin manifestations, was observed at a median of 2 months (range, 1–3).

The patient with hypereosinophilic syndrome achieved a partial response after 13.3 months of treatment.

Among patients with ECD, PET-based response assessment showed stable disease in two patients (50%), partial response in one patient (25%), and no response in one patient (25%). Three patients had diabetes insipidus at baseline without additional pituitary hormone deficiencies, and desmopressin requirements remained unchanged during PEG-IFN-α therapy. One patient developed nephrotic syndrome due to renal involvement of ECD and subsequently died during follow-up.

The patient with lymphomatoid granulomatosis received PEG-IFN-α as first-line therapy and achieved a partial response, which was followed by durable remission, leading to treatment discontinuation.

Patient characteristics, treatment details, clinical responses, and toxicity profiles of patients with Erdheim–Chester disease, primary myelofibrosis,

Table 1. Patient characteristics, treatment details, responses, and toxicity in PV, ET, CML, and SM

Characteristics	PV (n=12)	ET (n=6)	CML (n=2)*	SM (n=3)
Age, median (range)	47 (27–65)	30 (24–63)	52 (48–56)	47 (29–48)
Gender (F/M)	7 / 5	5 / 1	1 / 1	1 / 2
Previous treatments, median (range)	2 (1–3)	2 (1–3)	3	None
Indication for PEG-IFN-α	Resistance to HU/IFN: 6; Intolerance/toxicity: 6	Resistance to HU/ anagrelide: 3; Intolerance/ toxicity: 3	TKI suboptimal response: 1; Failure: 1	First-line
Duration of PEG-IFN-α, months (median, range)	15.9 (1–69.6)	21.5 (3–61.1)	31.5 (11.07–52.1)	12.1 (9.3–14.8)
Best response	CR: 5; PR: 6; NR: 1	CR: 5; NR: 1	MMR: 1; HR: 1	CI: 3
Time to best response, months (median, range)	4.1 (0.5–21)	7.3 (5.1–12.8)	2.3	Not applicable (subjective data)
Toxicity	Hair loss: 1; Nephropathy: 2; Myelosuppression: 1; Skin rash: 1; Flu-like symptoms: 1	Autoimmune thyroiditis: 1; Autoimmune hepatitis: 1	None	None
Reason for discontinuation	NR: 1; Toxicity: 6; Sustained remission: 1	NR/progression: 2; Sustained remission: 2	Sustained remission: 1	Sustained improvement: 2

* PEG-IFN-α was used in combination with TKI. CI, clinical improvement; CR, complete response; HR, hematologic response; HU, hydroxyurea; IFN, interferon; MMR, major molecular response; NR, no response; PR, partial response; TKI, tyrosine kinase inhibitor.

Table 2. Patient characteristics, treatment details, responses, and toxicity in ECD, PMF, HES, and LYG

Characteristics	ECD (n=4)	PMF (n=1)	HES (n=1)	LYG (n=1)
Age, median (range)	46.5 (23–73)	63	29	68
Gender (F/M)	2 / 2	1 / 0	0 / 1	0 / 1
Previous treatments	Cladribine in 1 patient; none in others	Hydroxyurea	Steroids	None
Indication for PEG-IFN-α	Non-response: 1; First-line: 3	Intolerance to hydroxyurea	First-line	First-line
Duration of PEG-IFN-α, months (median, range)	6.6 (2.53–28.6)	16.6	15	13.3
Best response	SD: 2; PR: 1; NR: 1	PR: 1	PR: 1	CR: 1
Time to best response, months (median, range)	6.6 (5.3–10.9)	8.1	13.3	12
Toxicity	None	None	None	None
Reason for discontinuation	Non-response: 1	–	Sustained remission: 1	Sustained remission: 1

* PEG-IFN-α was partially used in combination with chemotherapy. CR, complete response; HU, hydroxyurea; NR, no response; PR, partial response; SD, stable disease.

hypereosinophilic syndrome, and lymphomatoid granulomatosis are summarized in Table 2.

Toxicity and Treatment Discontinuation

Overall, treatment-related toxicity was observed in 26.6% of patients (n=8), resulting in permanent discontinuation of PEG-IFN-α in 20% (n=6). Reported adverse events included alopecia, skin rash, myelosuppression, nephropathy with nephrotic-range proteinuria, autoimmune thyroiditis, autoimmune hepatitis, and flu-like symptoms. No toxicity was observed in patients with SM, HES, ECD, or LYG.

DISCUSSION

In this retrospective, single-center study, we evaluated the real-world use of PEG-IFN-α across a heterogeneous cohort of patients with myeloproliferative neoplasms and rare hematologic disorders. Our findings suggest that PEG-IFN-α may demonstrate encouraging real-world activity in selected patients, particularly in PV and ET, although treatment discontinuation due to toxicity remains a significant limitation in routine clinical practice.

In PV and ET, our response rates (PV: CR 41.7%, PR 50%; ET: CR 83.3%) are broadly consistent with prior prospective studies reporting high hematologic response rates with pegylated interferons [2,16]. Quintás-Cardama et al. reported overall response rates exceeding 80% in both PV and ET, with higher complete response rates than those observed in our PV cohort; however, frequent partial responses in our patients resulted in a comparable overall disease control rate. In contrast, the high complete response rate observed in our ET patients closely mirrors that reported in prior prospective studies of PEG-IFN-α in ET [2]. More recent phase III trials further support the sustained disease-controlling potential of interferon-based therapies in PV. In the PROUD-PV and CONTINUATION-PV trials, ropeginterferon alfa-2b demonstrated increasing hematologic response rates over time and superior responses compared with hydroxyurea at longer follow-up, despite not meeting non-inferiority criteria at 12 months [17]. Although differences in interferon formulation and study design limit direct comparison, these data are consistent with the durable response patterns observed in our real-world cohort.

Similarly, the phase III trial by Mascarenhas et al. comparing PEG-IFN-α with hydroxyurea in high-risk PV and ET showed no significant differences in complete response or disease progression, while PEG-IFN-α was associated with greater molecular responses but a higher frequency of grade ≥3 adverse events [18]. Consistent with these findings, toxicity-related

treatment discontinuation occurred in a substantial proportion of PV patients in our cohort, underscoring that tolerability remains a key challenge of interferon-based therapy. The relatively high rate of treatment discontinuation due to intolerance or toxicity observed in patients with PV may reflect disease-specific treatment characteristics rather than an intrinsically unfavorable safety profile of PEG-IFN-α. In routine clinical practice, patients with PV often receive PEG-IFN-α over prolonged periods, frequently extending beyond the durations reported in prospective clinical trials. Consequently, longer follow-up and cumulative drug exposure may increase the likelihood of delayed or cumulative interferon-related adverse effects, ultimately leading to higher discontinuation rates. These real-world findings underscore the importance of long-term tolerability monitoring when PEG-IFN-α is used to control chronic disease in PV.

In CML, PEG-IFN-α was administered as an adjunct to tyrosine kinase inhibitors in selected patients with suboptimal responses, resulting in hematologic and molecular responses without treatment-limiting toxicity. These observations align with previous studies suggesting that interferon-based strategies may enhance molecular responses in chronic-phase CML when combined with TKI therapy, although their role has diminished in the era of highly effective TKIs [1,19].

Our findings also align with prior reports demonstrating heterogeneous responses to PEG-IFN-α across Philadelphia chromosome–negative myeloproliferative neoplasms. In a phase II study by Jabbour et al., response rates were highest in ET, while outcomes in PV and MF were more variable, and treatment discontinuation due to toxicity was common [20]. These results are consistent with our real-world experience and emphasize the importance of disease subtype and patient selection.

Data regarding PEG-IFN-α in rare hematologic and histiocytic disorders remain limited. In myelofibrosis, responses are generally less frequent and heterogeneous; our single MF patient achieved a partial response without toxicity, consistent with larger cohorts showing modest hematologic responses but potential clinical benefit in selected patients [21,22].

In hypereosinophilic syndrome, available evidence suggests favorable efficacy and tolerability, and our patient achieved sustained remission with PEG-IFN-α following corticosteroid failure, supporting its role as a steroid-sparing option in selected cases [23,24]. Consistent with the available literature, our single HES patient—initially responsive to corticosteroids but experiencing loss of response—achieved sustained remission after 15 months of PEG-IFN-α therapy without treatment-related complications, supporting its role as an effective steroid-sparing option in selected HES cases.

In systemic mastocytosis, interferon-based therapy is no longer routine first-line treatment but may remain useful for symptom control or cytoreduction in selected patients. All three SM patients in our cohort experienced rapid clinical improvement without treatment-limiting toxicity, supporting a potential role for PEG-IFN-α in carefully selected cases [25,26]. In this context, all three SM patients in our cohort received PEG-IFN-α as first-line therapy and experienced rapid clinical improvement, particularly in pruritus and cutaneous symptoms, with a median time to response of two months and no treatment-limiting toxicity.

Evidence for interferon-based therapy in lymphomatoid granulomatosis is mainly derived from studies using conventional IFN-α. In a pivotal phase II National Cancer Institute study, IFN-α-2b achieved high and durable response rates in low-grade disease, supporting its EBV-driven immunologic nature. Experience with PEG-IFN-α is limited to case reports; however, sustained responses with improved tolerability have been described [27]. Consistent with these reports, our single LYG patient achieved a partial response without significant toxicity, suggesting PEG-IFN-α as a feasible option in selected low-grade cases.

Interferon-based therapy has historically been the main systemic treatment for Erdheim–Chester disease, with evidence supporting improved survival and organ responses. In our cohort, PEG-IFN-α was used as initial therapy in all ECD patients, resulting in disease stabilization or partial response in most cases and no treatment-related toxicity. These findings are consistent with existing literature supporting PEG-IFN-α as an effective conventional option in selected ECD patients, while highlighting the need for alternative or targeted therapies in cases of progression [5,28].

This retrospective, single-center study is limited by the relatively small and heterogeneous sample size. Longer and more standardized follow-up and the inclusion of a comparator group could further strengthen

the assessment of treatment outcomes. In addition, molecular response and patient-reported outcomes were not systematically collected.

Lastly, but perhaps most importantly, our findings also illustrate that proven clinical effectiveness and acceptable toxicity profiles alone may not be sufficient to ensure sustained use of a therapeutic agent in contemporary clinical practice. PEG-IFN-α is not available in Türkiye today. Beyond clinical efficacy and safety, our findings also highlight a broader regulatory and access-related paradox surrounding interferon-based therapies in hematologic neoplasms. Despite decades of evidence demonstrating the disease-controlling and, in some settings, disease-modifying potential of IFN-α—particularly in classical myeloproliferative neoplasms —PEG-IFN-α remains largely unlicensed for most hematologic indications and has become increasingly difficult to access in many countries following the decline in its use for viral hepatitis. In contrast, structurally and biologically related formulations, such as ropeginterferon alfa-2b, have obtained regulatory approval for selected indications (e.g., PV) based on contemporary phase III trial programs. While differences in pegylation and pharmacokinetics exist, these developments reflect regulatory and developmental trajectories rather than a fundamental shift in interferon biology. Consequently, clinically similar interferon-based strategies may now be available under different formulations with substantially different cost and accessibility profiles. Real-world data, such as those presented in this study, remain important to contextualize the clinical value of PEG-IFN-α beyond formal licensing frameworks, particularly in rare diseases and in patient populations for whom alternative therapies are limited, contraindicated, or associated with long-term safety concerns.

In this single-center, real-world cohort, PEG-IFN-α demonstrated measurable clinical activity across a heterogeneous group of hematologic neoplasms, including both classical myeloproliferative neoplasms and selected rare entities. Response patterns varied by disease type, and treatment-related toxicity remained a relevant clinical issue, leading to discontinuation in a substantial proportion of patients. Despite its prolonged half-life and simplified dosing schedule, the overall tolerability profile of PEG-IFN-α was comparable to that reported for conventional interferon-α in previous studies. These findings suggest that PEG-IFN-α represents a feasible therapeutic option in selected patients, particularly in settings where alternative treatments are limited or contraindicated.

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Author contributions

Conception: A.B.B., Y.B.; Design: Y.B.; Data acquisition: A.B.B., Y.B.; Data analysis: A.B.B.; Data interpretation: A.B.B.; Drafting of the manuscript: A.B.B.; Critical revision of the manuscript: Y.B.. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Health Sciences Research Ethics Committee (Date: February 28, 2017, Decision/Protocol No: GO 17/206-03). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

Reconstructive strategies following Fournier's gangrene: A retrospective analysis of outcomes

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Abstract

Objective: Fournier's gangrene is a rapidly progressive and necrotizing infection of the perianal region and scrotum. Once clinical stabilization is achieved, the delayed reconstruction of the resultant defects can be planned. This study presents our institutional experience with reconstruction after Fournier's gangrene and discusses various surgical approaches along with their respective advantages and limitations.

Materials and Methods: A total of 21 patients were included in the study. The patients included in this study were older than 18 years with Fournier's gangrene and a minimal follow-up of 6 months postoperatively. Demographic and clinical variables, including mean age, defect size and location, comorbid conditions, time interval between initial debridement and reconstruction, type of reconstructive method used, postoperative hospital stay, and complication rates were analyzed.

Results: A total of 21 male patients aged 42-76 years with previously performed reconstruction following Fournier's gangrene. The defect most commonly involved the scrotum, and 68% of the scrotal skin was defective (38%–100%). Two patients had perineal involvement. Comorbidities were present in 86% of patients, most commonly diabetes mellitus. All patients received delayed surgical reconstruction after the appearance of healthy granulation tissue at the base of the wound. The mean time to reconstruction was 28.4 days (range, 15–56 days). The most commonly used reconstruction method was the scrotal flap alone (57%). The mean hospital stay after reconstruction was 7.2 days.

Conclusion: Fournier's gangrene is a rapidly progressive and fulminant necrotizing infection that requires prompt antibiotic therapy and aggressive surgical debridement. Reconstruction of soft tissue defects is essential for restoring functional and aesthetic integrity. The optimal approach should be individualized based on patient characteristics and defect features. Further comparative studies are required to refine the reconstructive strategies and improve the long-term outcomes.

Keywords: Fournier, gangrene, infection, reconstruction

Introduction

Fournier's gangrene is a rapidly progressive and fulminant form of necrotizing fasciitis that predominantly affects the scrotal, perianal, and genital regions. Fournier's gangrene predominantly affects males, with the scrotum being the most commonly involved site [1,2]. It is believed to result from a polymicrobial infection that advances to obliterative endarteritis with microthrombosis of the cutaneous and subcutaneous arterioles, leading to perifascial bacterial spread and subsequent gangrene of overlying tissues. Diabetes mellitus, alcoholism, obesity, and other states of immunosuppression are significant risk factors for Fournier's gangrene [3,4]. The diagnosis of Fournier's gangrene is primarily clinical in nature. Patients typically present with sudden onset of genital or perineal pain and swelling, accompanied by fever

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and systemic deterioration, which may rapidly progress to tissue necrosis with purulent discharge, crepitus or fluctuance, and ultimately septic shock [3,5].

Early diagnosis and prompt treatment are crucial in the management of Fournier's gangrene, as the disease progresses rapidly, is a true surgical emergency. Intensive fluid resuscitation, broad-spectrum intravenous antibiotic therapy, and urgent surgical exploration with aggressive debridement of all devitalized tissues are the cornerstones of treatment. Multiple debridement procedures are often required to achieve adequate source control and prevent further infection spread [6,7].

Reconstruction is planned after clinical stabilization and confirmed eradication of the infection, with the choice of technique largely determined by the size of the defect and the specific perineal tissue planes involved in the defect. Despite the many available reconstructive options, the overarching goal remains the restoration of functional integrity and satisfactory aesthetic outcome. For small and superficial defects in the perineal region, conservative wound care, primary closure, or split-thickness skin grafting may be sufficient. However, larger defects or those involving exposed vital structures generally require flap-based reconstructions [7,8].

Although a wide range of reconstructive options are available, no single technique is universally ideal or suitable for all cases. In this study, we present the patients in our center who underwent reconstructive surgery following Fournier's gangrene and discuss the reconstructive approaches presented in the current literature.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Ankara Training and Research Hospital (Review No. E-25/769). This retrospective review was performed for patients who underwent reconstruction following debridement for Fournier's gangrene at our institution between July 2023 and August 2025. The patients included in this study were older than 18 years with Fournier's gangrene and a minimal follow-up of 6 months postoperatively. The exclusion criteria were a prior history of testicular surgery and loss to follow-up. Demographic and clinical variables, including mean age, defect size and location, comorbid conditions, time interval between initial debridement and reconstruction, type of reconstructive method used, postoperative hospital stay, and complication rates, were analyzed. Informed consent was obtained from all patients before data collection.

RESULTS

A total of 21 male patients aged 42-76 years with previously performed reconstruction following Fournier's gangrene. The mean age of the patients was 54.2 years. The patient demographics and characteristics are listed in Table 1. The defect most commonly involved the scrotum, and 68% of the scrotal skin was defective (38%–100%). Two patients had perineal involvement as well. Comorbidities were present in 86% of patients, most commonly diabetes mellitus. In 3 patients (14%), we could not find any associated predisposing factor. All patients received delayed surgical reconstruction after the appearance of healthy granulation tissue at the base of the wound. The mean time to reconstruction was 28.4 days (range, 15–56 days). The most commonly used reconstruction method was the scrotal flap alone (57%) (Figure 1). Superomedial thigh flap was performed in six patients (29%) (Figure 2) ,and skin grafting was used in three patients (14%). The mean hospital stay after reconstruction was 9.2 days. One patient (4%) developed wound dehiscence and partial necrosis was seen in one patient (4%) and both were treated conservatively.

DISCUSSION

Fournier's gangrene is a fulminant necrotizing soft-tissue infection involving the scrotal, perianal, and perineal regions, characterized by rapid extension into the surrounding tissues and a high risk of mortality despite prompt intervention [6,9]. Although its pathophysiology is primarily attributed to polymicrobial infection comprising both aerobic and anaerobic bacteria, acting in conjunction with subcutaneous arteriolar microthrombosis to induce rapidly progressive necrosis, the exact etiology remains controversial [10]. While Fournier originally described cases without any identifiable predisposing factor and approximately one-quarter of contemporary cases similarly present with no clear underlying cause, most patients exhibit comorbidities that compromise immune function.

Table 1. Patient demographics and characteristics of injury

	n (%)
Gender	
Male	21 (100)
Female	0 (0)
Age (years)	
Mean	54.2
Range	42-76
Defect Location	
Scrotal	21 (100)
Perineal	2 (9.5)
Comorbidities	
Diabetes Mellitus	9 (42)
Hypertension	6 (29)
Renal Failure	3 (14)
Alcoholism	1 (4)
Time to reconstruction (day)	
Mean	28.4
Range	15-56
Reconstruction method	
Scrotal flap	12 (57)
Superomedial thigh flap	6 (29)
Skin graft	3 (14)
Hospital stays after reconstruction	
Mean	9.2
Range	5-19
Complication	
Wound dehiscence	1 (4)
Partial graft necrosis	1 (4)

Conditions such as diabetes mellitus, alcoholism, obesity, and other states of immunosuppression are well-recognized contributors that may facilitate the onset and accelerate the progression of the disease. Additionally, an identifiable initiating factor—such as colorectal pathology, perianal skin infection, or urinary tract infection—can be observed [6,11,12]. In the present study, diabetes mellitus was likewise the most frequently encountered comorbid condition, a finding that aligns closely with previously published literature. Published mortality rates range widely

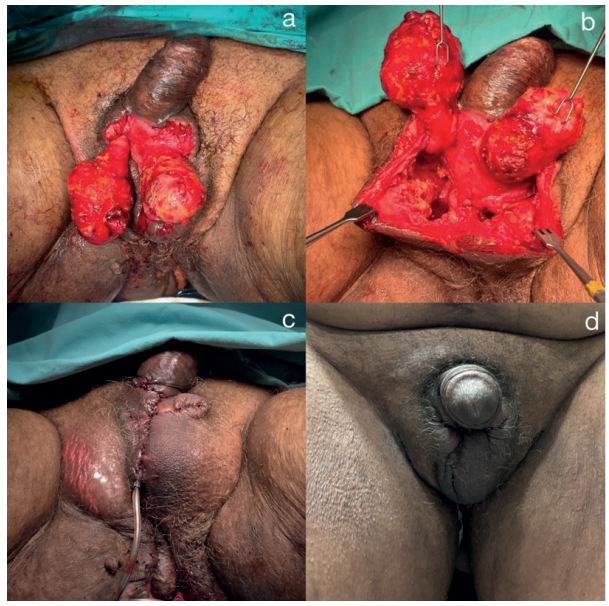

Figure 1. Reconstruction with scrotal flap after Fournier gangrene

a) Scrotal defect after Fournier gangrene
b) Intraoperative views of the scrotal flaps
c) Immediate postoperative result
d) Three-month post-operative result

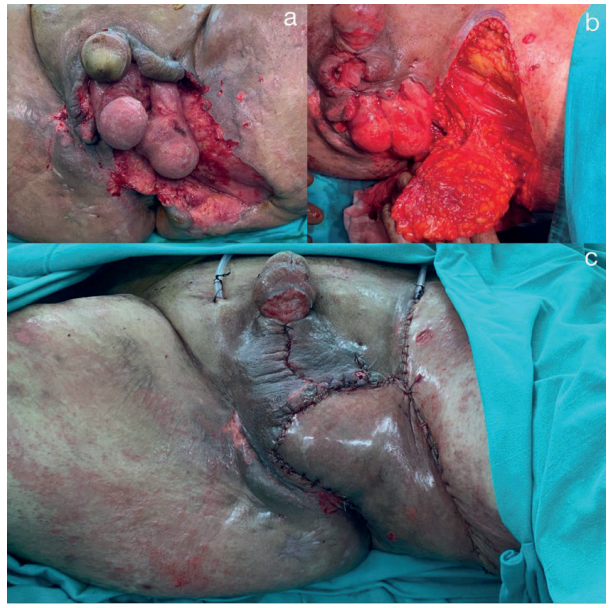

Figure 2. Reconstruction with superomedial thigh flap after Fournier gangrene

a) Scrotal and perineal defect after Fournier gangrene
b) Intraoperative views of the superomedial thigh flap
c) Immediate postoperative result

from 3% to 67%, reflecting heterogeneity in patient characteristics, treatment timing and disease severity. Collectively, these findings underscore the importance of early diagnosis, aggressive surgical debridement of necrotic tissue, broad-spectrum antimicrobial therapy and careful evaluation of patient-specific risk factors to optimize outcomes and guide ongoing discussions regarding the management of this life-threatening condition [1,13,14].

Once clinical stabilization is achieved and the infection is fully controlled, reconstruction of the resulting scrotal and perianal defects is necessary. Previous studies have reported an average interval of 33–35 days between disease onset and definitive reconstruction [1,3,15]. In the present study, this interval was little bit shorter, with a mean of 28.4 days, reflecting the time needed for adequate wound bed preparation and systemic stabilization. During this period, the patients were closely monitored by the urology department, and daily wound care was provided using conventional dressing methods or vacuum-assisted closure (VAC) therapy. VAC therapy has gained popularity following debridement, as it has been associated with reduced dressing-change frequency, decreased analgesic requirements, and—most notably—shorter hospital stays [16,17]. In the current study, the mean postoperative hospital stay following reconstruction was 7.2 days. According to the literature, the overall duration of stay at our institution was similar, suggesting that enhanced coordination with the urology department and integration of VAC therapy may help these outcomes and acceleration of the patient recovery and reduce hospitalization time [18,19].

The scrotum is the most frequently involved site in Fournier's gangrene, and consequently, post-infectious reconstruction is most commonly required in this region, with extension to the perianal area when necessary. Because the testes and spermatic cord receive their blood supply from sources distinct from the scrotal skin, they are generally spared from the necrotizing process and become exposed following the debridement of devitalized scrotal tissue. This anatomical preservation is clinically important because the testes maintain essential endocrine and reproductive functions, including testosterone production and spermatogenesis [1,6]. The optimal performance of these functions requires that the testes remain at a temperature lower than the core body temperature, underscoring the necessity of selecting reconstructive techniques that provide adequate protection and thermoregulation [20].

Reconstructive options for defects resulting from Fournier's gangrene include healing by secondary intention, primary closure, and various graft- or flap-based procedures. Because many patients present with significant comorbidities and are therefore considered high-risk surgical candidates, simple and single-stage reconstructive approaches are often preferred [7]. Primary closure can provide excellent functional and aesthetic outcomes; however, it is feasible only in very small defects where closure can be achieved without tension. Healing by secondary intention is another option for relatively limited defects or for patients with elevated anesthetic risk, although this approach is associated with prolonged healing times and an increased likelihood of wound contraction and deformity [3]. Skin grafts may be employed in cases where the tunica vaginalis remains intact and is adequately protected. However, their use is limited by challenges in graft adherence to the underlying tissues, which can compromise graft survival. In addition, skin grafts are generally less favored today because they provide fragile and insensate coverage, and graft contracture may lead to discomfort or even impaired testicular mobility, potentially causing dyspnea-like pain responses. However, cosmetic outcomes are often suboptimal [1,20]. Nevertheless, Tan et al. reported that grafts tend to soften within six months, eventually permitting testicular movement, and suggested that skin grafting remains a suitable option, particularly for elderly or comorbid patients, given the relative ease of the procedure and shorter operative duration compared with flap-based methods [21]. Scrotal flaps represent an excellent reconstructive option for small- to medium-sized scrotal defects, offering durable, high-quality coverage and favorable aesthetic outcomes while maintaining low donor-site morbidity (Figure 3). The technique is relatively straightforward and involves circumferential undermining of the remaining scrotal skin, effectively utilizing the inherent laxity and extensibility of the scrotum to achieve adequate tissue mobilization for defect closure [1,3]. In the present study, scrotal flaps were utilized in %57 of the patients with Fournier's gangrene. Currently, there is no consensus on the optimal reconstructive method for Fournier's gangrene, as multiple techniques can achieve satisfactory soft tissue coverage. These include

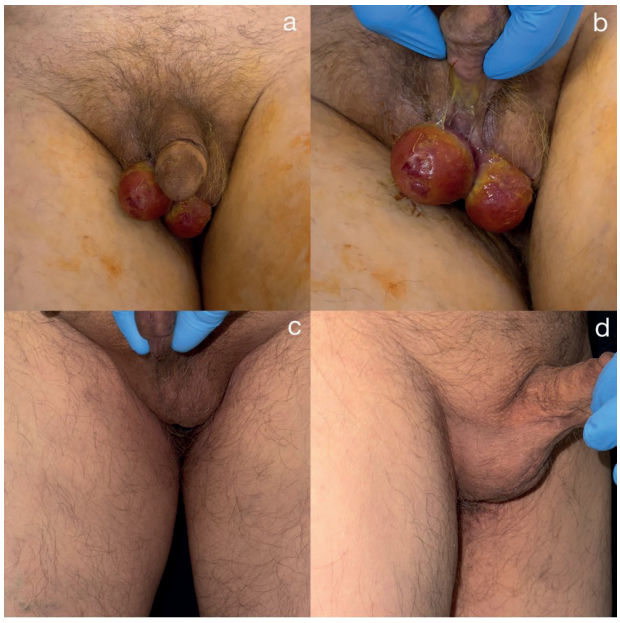

Figure 3. Reconstruction with scrotal flap after Fournier gangrene

a-b) Preoperative views Scrotal defect after Fournier gangrene

c-d) Postoperative 9-month result

split- or full-thickness skin grafts, local advancement flaps, scrotal flaps, fasciocutaneous flaps, muscle or myocutaneous flaps, perforator-based flaps, and testicular transposition in selected cases. Given the wide range of available reconstructive techniques, the optimal approach must be tailored to each patient. The selection of the most appropriate method should account for multiple factors, including the location and size of the defect, presence of cavitation, patient's overall medical status, age, and functional or aesthetic expectations, as well as the experience and technical preferences of the surgeon. Therefore, individualized decision-making remains essential for achieving successful outcomes in the reconstruction of Fournier's gangrene defects [1,3,6,22].

The limitations of this study include its retrospective design and single-center nature. Furthermore, the relatively small sample size represents an additional weakness that may affect the generalizability of the results.

CONCLUSION

Fournier's gangrene is a rapidly progressive and fulminant necrotizing infection that requires prompt antibiotic therapy and aggressive surgical debridement. Once infection control is achieved, early reconstruction of soft tissue defects is essential for restoring functional and aesthetic integrity. Although several reconstructive methods can yield satisfactory outcomes, no single technique is preferred for all patients. The optimal approach should be individualized based on patient characteristics and defect features. Further comparative studies are required to refine the reconstructive strategies and improve the long-term outcomes.

Author contribution

Conception and design: E.B.; Data acquisition: E.B.; Data analysis: E.B.; Data interpretation: E.B.; Drafting of the manuscript: E.B.; Critical revision of the manuscript: E.B.. The author reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Institutional Review Board of Ankara Training and Research Hospital (Date: January 15, 2026, Decision/Protocol No: Review No: E - 25/769). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The author declares that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The author declares that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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acta medica RESEARCH ARTICLE

Coercion in psychiatric inpatients with psychotic and mood disorders: Associations with trauma history, clinical characteristics, and short-term outcomes

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Abstract

Objectives: Coercive measures are interventions imposed against an individual's will and may be experienced as traumatic by psychiatric inpatients. This study aimed to examine the association between exposure to coercive measures and trauma burden in psychiatric inpatients, and to investigate the short-term relationship between coercive measures, posttraumatic stress symptoms, and treatment adherence.

Methods: The study included 60 patients hospitalized in a psychiatric ward. Trauma burden was assessed using the Childhood Trauma Questionnaire (CTQ) and the Cumulative Trauma Scale (CTS). Perceived social support, illness severity, and functioning were evaluated using standardized clinician-rated and self-report measures. One month after discharge, follow-up interviews were conducted to assess posttraumatic stress symptoms and treatment adherence. Patients exposed to coercive measures were compared with those not exposed.

Results: Patients exposed to coercive measures had significantly higher levels of childhood trauma and lifetime cumulative trauma burden. They also demonstrated more severe psychopathology, lower functioning, and lower perceived social support compared to patients not exposed to coercive measures. No significant differences were observed between the groups in posttraumatic stress symptoms or treatment adherence at short-term follow-up.

Conclusion: Psychiatric inpatients exposed to coercive measures represent a subgroup characterized by higher trauma burden and greater clinical vulnerability. Assessing trauma history and clinical characteristics may contribute to the identification of patients at increased risk for coercive interventions and support the implementation of trauma-informed care approaches.

Keywords: coercive measures, trauma, posttraumatic stress disorder, treatment adherence, involuntary treatment

Introduction

Coercion is a complex phenomenon that has long been at the center of both clinical practice and ethical and legal debates in the field of psychiatry. In its most general definition, it refers to an individual being subjected to an intervention against their will [1]. In psychiatric practice, coercion may be applied to manage acute agitation, aggressive behavior, or serious risk of self-harm. However, coercive interventions are not

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This study was derived from the medical residency thesis of Simge Ergün, titled "The effect of coercive measures on the risk of posttraumatic stress disorder and treatment compliance after discharge in patients hospitalized in psychiatric ward", conducted under the supervision of Ezgi İnce Guliyev at İstanbul University, Istanbul Faculty of Medicine, in 2024.

unique to psychiatry and are used in various conditions across different fields of medicine [2]. Official types of coercion include involuntary admission, involuntary treatment, seclusion, and chemical or mechanical restraint. Seclusion and restraint, in particular, are the subject of intense ethical debate because they directly restrict the individual's physical freedom of movement [1].

The frequency of coercion is reported to vary widely between countries and institutions. These differences are related not only to health systems and legislation, but also to the lack of standardization in the definition of coercion, heterogeneity in clinical practice, inadequacies in recording and reporting systems, and methodological difficulties [3]. This situation can lead to significant differences in practice, even between different hospitals within the same country.

Coercive measures are not only a form of clinical intervention but are also considered an ethical and legal issue that directly affects an individual's autonomy, freedom of movement, and physical integrity [4]. The approach that legitimizes these measures in certain situations is a paternalistic understanding grounded in the principles of "do no harm" and "do good." However, in clinical practice, the question of whether coercive measures benefit or harm the patient in the long term remains controversial. The literature suggests that such measures may be associated with impaired psychosocial functioning, worsening mental health symptoms, and reduced participation in community-based services [5]. It has been reported that coercive measures can be perceived as a traumatic experience by many patients and that post-traumatic stress symptoms may emerge after such measures [6].

Studies indicate that individuals who have been exposed to traumatic experiences, especially during childhood, may form a group that is more frequently exposed to coercion such as isolation or restraint in adulthood [7-10]. The type, frequency, and lifetime accumulation of traumatic experiences can create a cumulative effect that increases an individual's psychosocial vulnerability [11]. Recent research has shown that individuals who have experienced a traumatic event in the past may be at a significantly higher risk of isolation. Findings indicate that patients most frequently exposed to isolation and restraint measures are significantly more likely to have experienced physical or sexual abuse during childhood [12].

However, the reason why patients with a history of trauma are more frequently subjected to coercion has not yet been fully clarified. Factors that may be associated with coercion are thought to cluster in multiple areas, such as clinical indicators of violence, previous treatment and hospitalization history, and variables related to the social environment. However, studies that comprehensively address these variables are limited. The primary aim of this study was to examine whether there were differences in clinical, traumatic, and psychosocial characteristics between groups of inpatients in the psychiatric ward who were and were not subjected to coercive measures. As a secondary aim, the relationship between exposure to coercive measures and short-term post-traumatic stress symptoms and treatment compliance was investigated.

Materials and Methods

The study sample consisted of 30 individuals admitted to the inpatient ward of the Department of Psychiatry at Istanbul University Istanbul Faculty Medicine between January 2024 and June 2024 who had been diagnosed with a psychotic disorder or mood disorder according to DSM-5 and who had been subjected to at least one coercive measure (involuntary admission, isolation, mechanical restraint, chemical restraint) during their hospitalization; and met the inclusion criteria, and a group consisting of 29 patients who were not subjected to any coercive measures during their hospitalization and met the inclusion criteria. Exposure to coercive measures was determined retrospectively through a systematic review of discharge medical records. Documentation in nursing notes, physician progress notes, medication administration records, and discharge summaries was screened. When necessary, treating clinicians were contacted to clarify the indication for specific interventions. In the present study, chemical restraint was defined as the administration of psychotropic medication primarily for the purpose of rapid behavioral control (e.g., acute agitation, aggression, or imminent risk to self or others), rather than for routine therapeutic titration or scheduled pharmacological treatment. Medications administered as part of standard treatment were not considered chemical restraint unless explicitly documented as being used for behavioral control in an emergency context.

No a priori sample size calculation was performed, as the study employed a naturalistic, consecutive

sampling design based on inpatient admissions during the study period. However, similar observational inpatient studies examining coercive measures and trauma-related outcomes have reported comparable sample sizes, supporting the feasibility of research conducted in naturalistic psychiatric acute inpatient settings [13]. During the study period, all inpatients with mood or psychotic disorder diagnoses were screened for eligibility. Patients who did not meet the inclusion criteria or declined participation were excluded. The final sample consisted of patients who completed baseline assessments and follow-up evaluations. The research data collection process was approved by the Istanbul University Istanbul Faculty Medicine Clinical Research Ethics Committee (date: 12.01.2024, file no: 2023/2216) and conducted in accordance with the ethical principles outlined in the Helsinki Declaration. Participation was voluntary. After receiving verbal and written information about the study's purpose, methods, potential risks, and the rights of volunteers, participants who agreed to participate signed an Informed Consent Form. Patients who agreed to participate were clinically assessed according to DSM-5 to clarify their diagnoses and identify comorbidities. All patients were administered the forms and scales specified in the "Data Collection Tools" section. Information regarding the severity of the patients' hospitalization was obtained from the doctors who followed them during their stay, and two interviews were conducted upon discharge and one month after discharge. Each interview lasted an average of 50-60 minutes. To assess disease severity, the Clinical Global Impression Scale, Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale, and Hamilton Depression Scale were applied specifically for diagnosis. The Multidimensional Scale of Perceived Social Support, the Cumulative Trauma Scale, and the Childhood Trauma Scale were administered prior to hospital discharge. One month after discharge, the Treatment Adherence Scale and the Impact of Events Scale were administered. During these processes, a form was used to collect the patient's sociodemographic information, psychiatric history, hospitalization details, and post-hospitalization follow-up information.

The study included patients aged 18–65, literate, admitted to the psychiatric ward with a diagnosis of psychotic disorder or mood disorder according to DSM-5 diagnostic criteria, who agreed to participate in the study and signed a written informed consent form. Individuals with mental (e.g., significant cognitive impairment, intellectual disability) or physical (e.g., severe visual, hearing, or motor impairment) problems that would prevent them from completing the clinical interview or reliably understanding and completing the self-report scales were excluded from the study.

Data collection tools

Positive and Negative Syndrome Scale (PANSS): Developed by Kay and colleagues [14] to assess the severity of symptoms in schizophrenia patients. This tool comprises 30 items and includes a 7-item positive symptoms subscale, a 7-item negative symptoms subscale, and a 16-item general psychopathology subscale. Each item is scored on a scale of 1 to 7. The total score obtained from the scale ranges from 30 to 210, with higher scores indicating more severe psychopathological symptoms.

Young Mania Rating Scale (YMRS): Developed by Young et al. [15] to measure the severity of manic symptoms in patients. This 11-item scale, which inquires about manic symptoms experienced in the last 48 hours, is completed by the clinician based on the patient interview and observations made during the interview. Scores on the scale range from 0 to 60, with higher scores indicating more severe manic symptoms.

Hamilton Depression Rating Scale (HAMD): Developed by Hamilton to measure the severity of depressive symptoms in patients [16]. This 17-item scale, which assesses depressive symptoms experienced over the past week, is completed by the clinician based on the patient interview and observations made during the interview. Scores on the scale range from 0 to 52, with higher scores indicating more severe depressive symptoms.

Global Assessment of Functioning (GAF): This scale assesses an individual's overall level of functioning over a specific period. The assessment is usually based on the last week, and the clinician scores the patient based on the interview, information obtained from the patient's immediate environment, or medical records. The scoring system ranges from 0 to 100, where 0 represents the most severe impairment and 100 the highest level of functioning [17].

Cumulative Trauma Scale-Short Form (CTS-S): Developed by Kira and colleagues [18], the CTS-S assesses the cumulative impact of all traumatic experiences reported by the individual. The scale has

35 items, each scored on four dimensions: type of trauma, frequency of occurrence, age at occurrence, and assessment of the event's impact. Accepting a four-factor structure for trauma types, the subscales are defined as Survival Trauma, Personal Identity Trauma, Collective Identity Trauma, and Family Attachment Trauma. The Turkish validity and reliability study of the scale was conducted [11].

Childhood Trauma Questionnaire-28 (CTQ-28): This scale assesses traumatic experiences during childhood and adolescence, up to age 20 [19]. This 5-point Likert-type scale consists of 28 items and includes physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. High scores on each subscale indicate the possible presence of that type of maltreatment during childhood or adolescence. Subscale scores range from 5 to 25, and total scores range from 25 to 125. The validity and reliability of the scale in Turkish were examined by Şar and colleagues [20].

Multidimensional Scale of Perceived Social Support (MSPSS): Developed by Zimet et al. [21], the MSPSS assesses the extent to which an individual perceives social support from their environment. This 12-item scale is divided into three complementary subscales. Using a seven-point Likert-type scale, participants can score 1 for complete disagreement with a statement and 7 for complete agreement. Therefore, an increase in the score for any item indicates a corresponding increase in the perceived social support. An increase in the total score indicates that the person perceives the support resources around them as stronger. The Turkish adaptation was present [22].

Impact of Event Scale–Revised (IES-R): The IES-R includes seven additional items not found in the original IES, which relate to the hyperarousal symptoms of post-traumatic stress disorder (PTSD) [23]. The items correspond directly to 14 of the 17 DSM-IV symptoms of PTSD. Participants are asked to identify a specific stressful life event and then indicate how distressed or bothered they have been by each listed "difficulty" over the past seven days. Items are rated on a 5-point scale ranging from 0 to 4. The IES-R provides a total score (ranging from 0 to 88) and subscale scores for Intrusion, Avoidance, and Hyperarousal. The validity and reliability of the scale in Turkish were examined by Çorapçıoğlu et al [24].

Medication Adherence Reporting Scale (MARS): Developed by Horne and Weinman [25] to assess medication adherence, the MARS is a generic scale that can be customized by disease type. Participants are asked to indicate the frequency with which each of the 5 statements applies to them. The scale is rated on a 5-point Likert scale. The scores obtained from the scale range from 5 to 25. An increase in scores indicates compliance. The Turkish validity and reliability study was conducted [26].

Data analysis

Descriptive statistics results are presented as mean, standard deviation, percentage, and number. The normality of continuous variables was evaluated using the Shapiro–Wilk test and visual inspection of histograms and Q–Q plots. For variables following a normal distribution in the comparison of two independent groups, the independent variables t-test was used. For the comparison of categorical variables, the Pearson Chi-square test was used, and Fisher's exact test was used when more than 20% of cells had expected counts <5. For statistical significance, unless otherwise specified, a type I error rate below five percent ($p<0.05$) was accepted. Statistical analyses were performed using IBM SPSS (Statistical Package for Social Sciences) 29 software.

Results

A total of 60 patients, 33 men and 27 women, were included in the study. Thirty-one of these patients formed the group that was subjected to at least one coercive/involuntary medical practice during their hospital stay, while 29 formed the group that was not subjected to any coercive measures. The sociodemographic characteristics of both groups are presented in Table 1. No significant differences were found between the groups in terms of age, years of education, gender, marital status, and employment status.

Regarding diagnostic distribution, 26 patients (43.3%) were diagnosed with a primary psychotic disorder, and 34 patients (56.7%) with a mood disorder. Among patients with psychotic disorders, 19 met criteria for schizophrenia, 6 for unspecified schizophrenia spectrum and other psychotic disorder, and 1 for substance/medication-induced psychotic disorder. Among patients

Table 1. Comparison of patients' sociodemographic and clinical data

	Total (n=60)	Coercive Measures (+) (n=31)	Coercive Measures (-) (n=29)	t*	p
	mean±SD	mean±SD	mean±SD		
Age, *years*	36.91±13.04	35.96±12.88	37.93±13.37	0.579	0.565
Education, *years*	11.71±4.44	12.48±3.54	10.89±5.17	1.377	0.175
Duration of Hospitalization, *days*	25.25±11.80	28.19±13.07	22.10±9.52	2.050	**0.045**
Duration of Illness, *months*	137.28±123.00	127.15±117.88	147.72±129.50	0.633	0.529
Previous hospitalization	2.76±3.28	3.63±3.76	1.86±2.46	2.146	**0.037**
	n (%)	n (%)	n (%)	X2 †	p
Gender, *female*	27 (45.0)	14 (45.2)	13 (44.8)	0.001	0.979
Marital Status, *married*	21 (35.0)	9 (29.0)	12 (41.3)	1.034	0.596
Working, *yes*	19 (31.7)	10 (32.3)	9 (31.0)	2.031	0.362
Income, *low*	27 (45.0)	16 (51.6)	11 (37.9)	1.461	0.482
Diagnosis, *psychotic disorder*	26 (43.3)	13 (41.9)	13 (44.8)	1.529	0.466
Psychotic symptom, *present*	44 (73.3)	22 (70.9)	22 (75.9)	0.184	0.668
Suicide ideation at admission, *present*	25 (41.7)	12 (38.7)	13 (44.8)	0.231	0.631
Homicidal ideation at admission, *present*	22 (36.7)	16 (51.6)	6 (20.7)	6.170	**0.013**
Insight at admission, *absent*	41 (68.3)	26 (83.8)	15 (51.7)	7.165	**0.028**

* Independent samples t-test and †chi-square test were used. Statistical significance was set at $p < 0.05$. SD = standard deviation.

with mood disorders, 30 were diagnosed with bipolar disorder with the following current episode specifiers: 13 met criteria for bipolar disorder, current manic episode with psychotic features, 3 for bipolar disorder, current major depressive episode with psychotic features, 4 for bipolar disorder, current major depressive episode without psychotic features, 7 for bipolar disorder, current manic episode without psychotic features, and 3 for bipolar disorder, current manic episode with mixed features. The remaining 4 patients met criteria for major depressive disorder. Of the patients, 41.7% were involuntarily admitted to the hospital, 31.7% were isolated, 23.3% were subjected to mechanical restraint, and 33.3% were subjected to chemical restraint. Of the patients subjected to coercive measures, 32.3% were subjected to one measure, 19.4% to two measures, 12.9% to three measures, and 35.5% to four different measures. The mean number of coercive measures was 2.51±1.59.

Comparison of clinical characteristics

Findings regarding clinical characteristics are presented in Table 1 and Table 2. The total length of stay was significantly longer in patients subjected to coercive measures (28.19±13.07 days vs. 22.10±9.52 days; p=0.045). The rate of homicidal thoughts at the time of hospital admission was also significantly higher in the coercive measures group (72.7% vs. 27.3%; p=0.013). Of the 22 patients with a history of homicidal behavior, 18 (81.8%) were in the coercive measures group, and this difference is statistically significant (p=0.001).

Eleven of the 14 patients with a history of substance use (78.6%) were in the coercive measures group, and the difference between the groups was significant (p=0.021). The level of insight during hospitalization was significantly lower in the group exposed to coercive measures (p=0.028). Furthermore, previous experiences

of involuntary hospitalization, seclusion, mechanical restraint, and chemical restraint were significantly more common in this group (p=0.003, p=0.011, p=0.001, and p=0.007, respectively). The number of previous hospitalizations was also significantly higher in the group exposed to coercive measures (p=0.037).

The results of the scales related to disease severity and functioning are presented in Table 3. In the group exposed to coercive measures, global functioning at admission (p=0.004), and depression scores (p=0.001) were found to be significantly lower. In contrast, PANSS positive and YMRS scores were significantly higher (p=0.007 and p=0.015, respectively).

Table 2. Comparison between groups in terms of past clinical history

	Total (n=60)	Coercive Measures (+) (n=31)	Coercive Measures (-) (n=29)	X^2 *	p
	n (%)	n (%)	n (%)		
History of involuntary hospitalization, *present*	24 (40.0)	18 (58.1)	6 (20.7)	8.721	**0.003**
History of isolation, *present*	20 (33.3)	15 (48.4)	5 (17.2)	6.541	**0.011**
History of mechanical restraint, *present*	18 (30.0)	15 (48.4)	3 (10.3)	10.320	**0.001**
History of chemical restraint, *present*	23 (38.3)	17 (54.8)	6 (20.7)	7.392	**0.007**
History of medication non-adherence, *present*	38 (63.3)	20 (64.5)	18 (62.1)	0.039	0.844
History of suicide attempt, *present*	18 (30.0)	8 (25.8)	10 (34.5)	0.537	0.464
History of self-harming behavior, *present*	31 (51.7)	18 (58.1)	13 (44.8)	1.051	0.305
History of homicidal behavior, *present*	22 (36.7)	18 (58.1)	4 (13.8)	12.646	**<0.001**
Lifetime history of alcohol use, *present*	7 (11.7)	4 (12.9)	3 (10.3)	0.095	0.758
Lifetime history of substance use, *present*	14 (23.3)	11 (35.5)	3 (10.3)	5.293	**0.021**
History of psychiatric disorder in first-degree relatives, *present*	18 (30.0)	10 (32.3)	8 (27.6)	0.156	0.693

*Chi-square test was used. Statistical significance was set at $p < 0.05$. n = number.

Table 3. Comparison of clinical scales assessing disease severity, functionality, and improvement

		Total (n=60)	Coercive Measures (+) (n=31)	Coercive Measures (-) (n=29)	t*	p
		mean±SD	mean±SD	mean±SD		
GAF at admission		25.86±9.94	22.38±9.12	29.58±9.56	2.983	**0.004**
GAF at discharge		70.85±15.13	69.06±15.31	72.75±14.97	0.944	0.349
PANSS						
	Positive	21.35±10.59	24.87±11.64	17.58±7.91	2.814	**0.007**
	Negative	17.06±9.12	16.25±10.29	17.93±7.75	0.714	0.479
	General	41.30±9.95	43.29±11.11	39.17±8.21	1.623	0.110
	Total	79.38±23.22	83.77±27.19	74.68±17.32	1.553	0.127
YMRS		12.77±17.19	18.39±19.01	7.34±13.43	2.526	**0.015**
HAMD		11.44±11.84	6.44±8.84	17.13±11.52	3.432	**0.001**

*Independent samples t-test was used. Statistical significance was set at $p < 0.05$. Higher scores in GAF indicate better functioning, while higher scores in PANSS, YMRS and HAMD indicate greater symptom severity. GAF, Global Assessment of Functioning; HAM-D, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; YMRS, Young Mania Rating Scale.

Comparison of past traumatic experiences and social support

Both childhood traumas (CTQ total and all subscales; all p<0.01) and lifetime cumulative trauma load (CTS total and frequency; all p<0.001) were significantly higher in the group exposed to coercive measures (Table 4). The family subscale (p=0.012) and total score (p=0.011) of the MSPSS were significantly lower in the group exposed to coercive measures.

Follow-up results

At the one-month follow-up, no significant differences were found between the two groups in terms of post-traumatic stress symptoms (IES–R score) and treatment compliance (Table 4).

Table 4. Comparison of traumatic experiences, social support, and medication adherence between groups

		Total (n=60)	Coercive Measures (+) (n=31)	Coercive Measures (-) (n=29)		
		mean±SD	mean±SD	mean±SD	t*	p
CTS						
	Survival	1.48±1.20	1.90±1.32	1.03±0.86	3.025	**0.004**
	Personality	2.30±2.14	3.67±2.13	0.82±0.71	7.027	**<0.001**
	Collective	0.56±0.87	0.83±1.03	0.27±0.52	2.677	**0.010**
	Family	1.75±1.29	2.29±1.27	1.17±1.07	3.672	**<0.001**
	Total	6.11±4.06	8.74±3.83	3.31±1.81	7.079	**<0.001**
	Frequency	14.73±12.48	22.45±12.52	6.48±4.88	6.583	**<0.001**
CTQ						
	Physical abuse	6.91±3.75	8.25±4.19	5.48±2.59	3.101	**0.003**
	Physical neglect	7.61±3.50	9.09±3.90	6.03±2.14	3.799	**<0.001**
	Emotional abuse	9.33±5.30	11.77±5.48	6.72±3.65	4.220	**<0.001**
	Emotional neglect	12.63±5.09	15.54±4.51	9.51±3.66	5.659	**<0.001**
	Sexual abuse	6.53±3.30	7.51±3.83	5.48±2.24	2.524	**0.015**
	Total	42.80±17.26	51.80±17.43	33.17±10.81	5.010	**<0.001**
MSPSS						
	Family	20.95±6.13	19.06±6.90	22.96±4.47	2.612	**0.012**
	Friend	14.80±8.15	12.83±7.69	16.89±8.24	1.972	0.053
	Significant other	9.01±6.42	7.58±6.13	10.55±6.47	1.826	0.073
	Total	44.75±16.97	39.45±16.76	50.41±15.54	2.621	**0.011**
IES–R		0.16±0.83	0.10±0.40	0.24±1.12	0.648	0.520
MARS		24.77±1.06	24.63±1.47	24.93±0.25	1.089	0.284

*Independent samples t-test was used. Statistical significance was set at p < 0.05. For CTS, CTQ, and IES-R, higher scores indicate worse trauma burden. For MSPSS, higher scores indicate better social support and for MARS higher scores indicate better compliance. CTQ, Childhood Trauma Questionnaire; CTS, Cumulative Trauma Scale; IES-R, Impact of Event Scale–Revised; MARS, Medication Adherence Reporting Scale; MSPSS, Multidimensional Scale of Perceived Social Support; SD, standard deviation.

Discussion

This study examined the exposure to coercive measures, past trauma burden, clinical characteristics, and psychosocial variables in patients hospitalized in the psychiatry ward with diagnoses of psychotic and mood disorders. The findings show that patients exposed to coercive measures had higher childhood and lifetime trauma burdens and presented a more severe clinical picture. In contrast, no significant difference was found between exposure to coercion and post-traumatic stress symptoms and treatment compliance in the short-term follow-up. These findings indicate that the complex relationship between coercion , trauma history, and clinical severity must be addressed holistically.

Our findings from the Cumulative Trauma Scale (CTS) and Childhood Trauma Questionnaire (CTQ) indicate that patients exposed to coercive measures have a higher past trauma burden. This finding is consistent with previous studies pointing to a relationship between past traumatic experiences and exposure to coercive measures [7,8,12,27]. The literature reports that traumatic experiences in childhood may have negative effects on social functioning and emotional regulation skills [28]. Furthermore, a history of childhood maltreatment has been shown to be associated with aggressive behavior and self-harm tendencies in adulthood [29]. It is thought that these characteristics may be seen alongside a clinical picture that could complicate management during hospitalization in psychiatric services, and that this situation may correspond to the profile of patients subjected to coercive measures. In our study, the more frequent occurrence of a history of harmful behavior toward others and thoughts of harming others during hospitalization in the group subjected to coercive measures can be evaluated within this framework. However, due to the cross-sectional design of the study, it is not possible to claim that exposure to coercive measures is a direct result of past traumatic experiences or that these measures lead to new traumatic experiences. In our study, patients exposed to coercive measures were also more frequently exposed to similar measures during their previous hospitalizations, which is consistent with findings reported in the literature [8]. However, this situation should be considered a reflection of a more complex clinical context involving clinical severity, disease course, and previous hospitalization experiences, rather than a causal cycle. In this context, it remains unclear whether repeated exposure to coercive measures reflects the traumatic impact of prior restrictive interventions or whether patients with more severe and persistent psychopathology are inherently more likely to be exposed to such measures over time. The present study cannot disentangle these possibilities. Future research should therefore aim to examine this question using longitudinal designs with larger samples and a more comprehensive assessment of potential clinical and environmental confounders.

Our study also addressed collective identity traumas, unlike previous research. Collective identity traumas, such as forced migration, immigration, and exposure to discrimination due to ethnic origin or sexual identity, were reported more frequently in the group exposed to coercive measures. The literature indicates that disadvantaged groups may be more likely to experience different types of traumatic experiences throughout their lives and may be in a more vulnerable position in terms of access to psychiatric services and treatment processes [8,30]. Our findings suggest that collective identity–related traumatic experiences may represent an additional layer of vulnerability among patients exposed to coercive measures; however, the mechanisms underlying this association require further investigation.

The literature includes a study examining whether exposure to any type of trauma, as well as the frequency of exposure to trauma, may be associated with exposure to coercive measures [12]. In our study, the frequency of exposure to trauma was also evaluated with the CTS, and it was found that the frequency of trauma was higher in patients exposed to coercive measures. This finding indicates that not only the presence of traumatic experiences but also their repeated occurrence throughout life should be considered in conjunction with the clinical picture. The Developmentally Based Trauma Framework (DBTF) emphasizes the importance of considering dimensions such as severity, frequency, and chronicity together when assessing the effects of trauma on individuals [18]. The findings obtained in our study are consistent with this conceptual framework.

Comparisons of clinical characteristics revealed that patients exposed to coercive measures had a more frequent history of substance use and more pronounced disease severity. In this group, PANSS positive subscale, and Young Mania Rating Scale (YMRS) scores were found to be higher compared to patients not exposed to coercive measures, although depressive symptom severity was lower. The literature reports that positive

psychotic symptoms, the severity of manic and depressive symptoms, can be seen in conjunction with a picture that complicates the clinical course and makes in-service management difficult [31,32]. The literature emphasizes that a history of substance use may also accompany this clinical picture and complicate clinical management during hospitalization [33]. Exposure to coercive measures during hospitalization is predicted by the presence of the most aggressive behaviors and hostility [2,34]. In this context, the clinical findings obtained in our study suggest that the group of patients exposed to coercive measures exhibited a more severe and complex clinical picture.

Our study also found that perceived social support, particularly family support, was lower in patients exposed to coercive measures. Social support is considered an important psychosocial variable that can reduce the negative effects of traumatic experiences on mental health [35]. Previous research has shown that perceived social support may be more limited in individuals with a history of trauma and that these individuals may encounter more psychosocial difficulties throughout their lives [36,37]. The results obtained in our study suggest that lower levels of social support in patients exposed to coercive measures should be evaluated in conjunction with the clinical and psychosocial vulnerability of this patient group.

Our short-term follow-up findings showed no significant difference between exposure to coercive measures and post-traumatic stress symptoms. Although studies in the literature report that coercive measures may increase the risk of post-traumatic stress symptoms [7-10], some longitudinal studies have shown that such a relationship does not exist or may weaken over time [38,39]. In our study, the low level of post-traumatic stress symptoms may be related to regular and structured interviews with patients during their hospital stay and close follow-up after discharge. Providing a safe therapeutic environment and a continuous follow-up process after discharge may contribute to mitigating the possible negative psychological effects of coercive measures.

Our findings regarding treatment compliance indicate that there is no significant difference in short-term treatment compliance between patients exposed to coercive measures and those who are not. The literature on this subject presents conflicting results; while some studies report that coercive measures may negatively affect treatment compliance [40], others have not found a similar effect [5]. The high treatment compliance found in both groups in our study may reflect the structured treatment environment provided by the service conditions and the therapeutic relationship maintained after discharge. However, evaluating treatment compliance with longer-term follow-up will contribute to a clearer understanding of this relationship.

Overall, from a clinical and ethical perspective, our findings underscore the importance of trauma-informed care approaches in psychiatric inpatient settings. Recognizing patients' trauma histories and psychosocial vulnerabilities may help guide the use of least-restrictive interventions and support efforts to minimize exposure to coercive measures.

One of the strengths of our study is that it included a comprehensive assessment covering not only the presence of past traumatic experiences but also their different types and frequency. Furthermore, the consideration of collective identity traumas alongside exposure to coercive measures is a distinguishing feature of our study. On the other hand, several limitations should be considered when interpreting the study's findings. The limited sample size and the non-homogeneous distribution of diagnostic subgroups represent important constraints; therefore, the findings need to be re-evaluated in larger, more diverse clinical samples. In addition, the single-center design and the inclusion of inpatients hospitalized within a specific time window limit the generalizability of the results. Due to the observational nature of the study, causal inferences regarding the association between exposure to restrictive measures and trauma history cannot be established, and residual confounding related to unmeasured or inadequately measured clinical or environmental factors may remain. It should be noted that the coercive measures included in this study differ in their clinical indications and levels of perceived intrusiveness. However, given the limited sample size, these measures were conceptualized as a composite exposure to reflect overall coercive experience during hospitalization. Future studies with larger samples may allow for the examination of differential effects of specific coercive measures. Finally, trauma history was assessed using self-report measures, which may be subject to retrospective recall bias; moreover, as trauma-related symptom measures were not anchored to a clearly defined index event, the interpretability of the findings may be reduced.

In conclusion, this study found that both the presence and frequency of cumulative trauma load showed significant differences between patient groups exposed to coercive measures and those who were not. Patients exposed to coercive measures were found to have a higher number of previous hospitalizations, thoughts of harming others during hospitalization, a history of harmful behavior toward others, a history of substance use, and previous coercion experiences; clinical severity was higher, and perceived social support was lower. In contrast, in the short-term follow-up, post-traumatic stress symptoms were found to be low, and treatment compliance was high in both groups. These findings suggest that the combined assessment of trauma history, clinical characteristics, and social support levels in hospitalized psychiatric patients may contribute to a better understanding of the profile of patients exposed to coercive measures.

Author contributions

Conception and design: S.E., E.I.G.; Data acquisition: S.E.; Data analysis: E.I.G.; Data interpretation: S.E., E.I.G.; Drafting of the manuscript: S.E.; Critical revision of the manuscript: E.I.G. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: January 12, 2024, Decision/Protocol No: 2023/2216). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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CASE REPORT

Pulmonary thromboembolism presenting with multiple cavitary infarcts: A diagnostic challenge with overlap to granulomatous vasculitis

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Abstract

Pulmonary embolism (PE) is a life-threatening condition that can present with a wide range of symptoms, often complicating its diagnosis. Pulmonary infarction (PI), a rare consequence of PE, may mimic other conditions such as pneumonia, malignancy, or vasculitis. A 65-year-old woman presented with progressive dyspnoea, chest pain, and haemoptysis. She was initially diagnosed with pneumonia; however, imaging revealed cavitating pulmonary infarcts. Further investigations excluded tuberculosis, fungal and viral infections, as well as granulomatosis with polyangiitis presenting with multiple cavitary lesions. Contrast-enhanced CT pulmonary angiography confirmed the diagnosis of PE with multiple cavitary infarcts. The patient was treated with anticoagulation and broad-spectrum antibiotics, resulting in complete clinical and radiological resolution within eight months. This case highlights the importance of considering infected cavitary pulmonary infarction in the differential diagnosis of rapidly cavitating pulmonary lesions, particularly in the presence of clinical signs of infection, to avoid misdiagnosis and ensure appropriate management.

Keywords: pulmonary embolism, pulmonary infarction, cavitation, sepsis, differential diagnosis

Introduction

Pulmonary embolism (PE) is a potentially life-threatening condition caused by sudden obstruction in the pulmonary circulation, leading to impaired perfusion and possible parenchymal ischemia. It carries considerable morbidity and mortality, with fatality rates reported between 10% and 28% when diagnosis or treatment is delayed [1,2], highlighting the need for early recognition.

Common symptoms include dyspnea, pleuritic chest pain, and hypoxemia, though presentations can be nonspecific. Pulmonary infarction (PI), a consequence of distal arterial occlusion in PE, occurs in 10% to 30% of cases [1,3], despite dual pulmonary and bronchial arterial supply. Diagnosis may vary based on clinical, imaging, or pathological findings.

Infarcts typically appear as non-cavitating opacities; however, cavitation may develop, particularly in infected or immunocompromised cases. Postmortem data suggest cavitation occurs in 4–5% of pulmonary infarcts [4], potentially from sterile necrosis or secondary infection [5]. Cavitating infarctions can mimic infections, malignancies, or vasculitides like granulomatosis with polyangiitis (GPA), making diagnosis challenging [6,7]. A multidisciplinary approach is essential. We present a rare case of histologically confirmed septic cavitary pulmonary infarction initially resembling GPA.

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CASE HISTORY

A 65-year-old woman presented with a two-month history of progressive dyspnea, productive cough, chest discomfort, and intermittent hemoptysis. She reported yellowish sputum with recent blood-tinging and sharp chest pain. Her history included type 2 diabetes, hypertension, and prior coronary stenting. There was no smoking, tuberculosis (TB) exposure, or occupational risk.

On exam, she had bilateral (2+) pretibial edema and reduced breath sounds. SpO_2 was 92% on 3 L/min oxygen, and temperature was 38.2°C. Labs showed leukocytosis (white blood cell count [WBC] 17,100/mm^3; neutrophils 16,000/mm^3), C-reactive protein (CRP) 272 mg/L, hemoglobin A1c (HbA1c) 13.5%, and postprandial glucose 355 mg/dL. Urine studies showed nephrotic-range proteinuria (1297 mg/day) and low spot urine sodium (11 mmol/L).

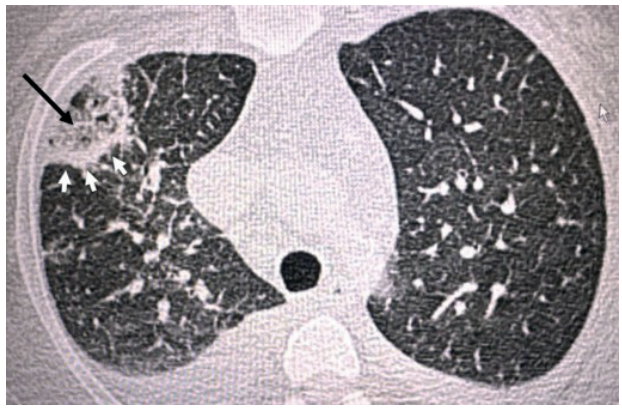

Figure 1. On non-contrast axial chest CT, a pleural-based, triangular consolidation (white arrows) is noted in the anterior segment of the right upper lobe, demonstrating smooth margins and a central ground-glass component (black arrow), raising suspicion for pneumonic infiltration.

Initial chest X-ray demonstrated blunting of the bilateral costophrenic angles and an ill-defined opacity in the mid-lung zone. Because pneumonia was suspected, a non-contrast chest CT was obtained, revealing bilateral pleural effusions and a wedge-shaped consolidation in the anterior right upper lobe with central ground-glass changes adjacent to the pleura (Figure 1). Empiric Sulbactam/Cefoperazone together with intravenous furosemide was initiated. Despite appropriate treatment, the patient showed no clinical improvement by the third day, prompting a switch to Piperacillin/Tazobactam. On the seventh day, she developed a new fever (37.9°C), and *E. coli* grew in blood and sputum cultures; therefore, Meropenem was started. During this period, a markedly elevated D-dimer level (2620 ng/mL) was noted. Given the persistent lack of clinical response to broad-spectrum antibiotics together with the unexpectedly high D-dimer, pulmonary embolism became a significant diagnostic consideration. On the twelfth day, a computed tomography pulmonary angiogram (CTPA) was performed and demonstrated cavitation within the right upper-lobe consolidation as well as newly developed cavitary lesions in the left lower and right lungs (Figure 2). Segmental and subsegmental pulmonary arteries in both upper lobes and in the distal left lower lobe showed intraluminal filling defects consistent with thromboembolic occlusion (Figure 3). The patient had multiple recognized factors for pulmonary thromboembolism, including advanced age, poorly controlled diabetes mellitus, acute systemic infection with bacteremia, and proteinuria attributed to diabetic nephropathy, all of which may have contributed to a prothrombotic state.

A detailed diagnostic evaluation excluded tuberculosis, fungal and viral infections (negative serology and bronchoalveolar lavage (BAL) cultures), and systemic autoimmune or vasculitic diseases (negative antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) panel). The coexistence of multiple cavitary pulmonary lesions and bacteremia prompted evaluation for infective endocarditis; however, transthoracic echocardiography was unremarkable, with no evidence of valvular vegetations or structural abnormalities. Proteinuria and hyponatremia were attributed to diabetic nephropathy, and upper respiratory tract examination, including sinus CT, showed no abnormalities. Despite the radiological diagnosis of pulmonary embolism, the rapid progression of multiple cavitary lesions, their atypical upper-lobe predominance, and the rarity of cavitation in pulmonary infarction raised persistent concern for alternative diagnoses, particularly vasculitis. Therefore, tissue sampling was pursued to exclude granulomatosis with polyangiitis and other inflammatory or malignant processes.A CT-guided transthoracic core-needle biopsy (CT-TTNB) showed acute inflammation and

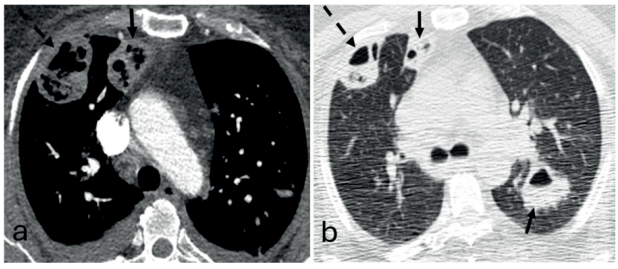

Figure 2. Cavitation has developed in the previously observed consolidation in the right upper lobe (dashed black arrow). New cavitary lesions are seen adjacent to the first lesion and in the superior segment of the left lower lobe (black arrows). These findings are demonstrated in both the mediastinal (a) and parenchymal (b) windows.

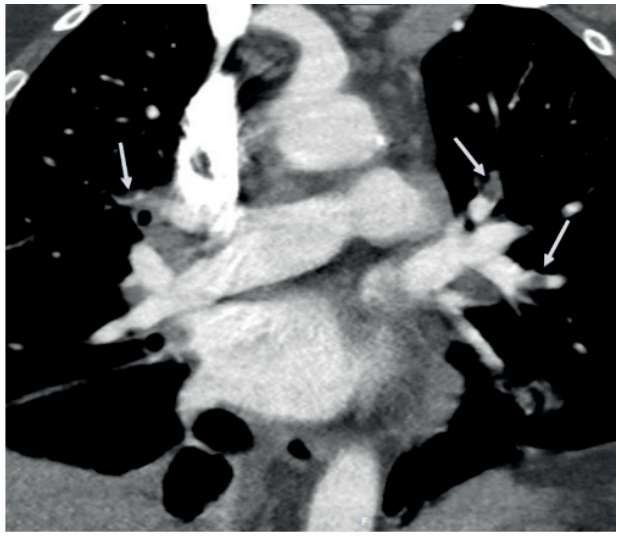

Figure 3. Contrast-enhanced pulmonary CT angiography shows filling defects compatible with thromboembolism in the segmental branches of both pulmonary arteries in the upper lobes and in the left lower lobe branch (arrows).

focal fibrosis, but no vasculitis. The final diagnosis was pulmonary embolism with multiple pulmonary infarcts. Persistent inflammation, E. coli growth in blood/sputum cultures, and rapid cavitation supported septic pulmonary infarction. Enoxaparin was started, later replaced by oral rivaroxaban. The CT performed at 8 months showed complete resolution of the cavitary lesions with minimal remaining fibrosis.

DISCUSSION

Pulmonary embolism is a critical cardiovascular emergency with variable presentations, complicating diagnosis. Pulmonary infarction, although uncommon, may present with hemoptysis or pleuritic pain. Incidental PE is more often detected without infarction (35%) than with infarction (11%) [1]. PI is frequently reported in delayed PE because of its resemblance to pneumonia or vasculitis [6,7]. In this case, initial imaging suggested pneumonia; however, lack of response to treatment prompted CTPA on day 12, revealing multiple cavitary consolidations. Final diagnosis of PI was confirmed by histopathology.

On CT, the classic radiographic finding of pulmonary infarction (PI)—Hampton's hump—has limited value. Instead, peripheral consolidations with central low attenuation and hypoenhancement on contrast-enhanced scans are more specific, reported in approximately 98% and 95% of cases, respectively [8,9]. Cavitation remains rare[4,10]. In this case, atypical imaging findings prompted further evaluation. Differential diagnoses for multiple cavitary lung lesions include infectious processes such as septic pulmonary embolism and vasculitis [3,7].

GPA was initially suspected due to overlapping imaging features with pulmonary infarction, including wedge-shaped morphology and angiocentric distribution [11]. However, GPA lesions typically show peribronchovascular distribution, irregular margins, and heterogeneous enhancement [12], unlike the subpleural, smooth-bordered, non-enhancing, and rapidly cavitating lesions seen in this case. Together with negative vasculitis markers, these findings favored septic pulmonary infarction secondary to untreated PE. CTPA confirmed PE by revealing central and segmental arterial filling defects with multiple infarcts. Comprehensive clinical, laboratory, imaging, and histopathological evaluation showed no evidence of systemic vasculitis, effectively excluding GPA.

Septic pulmonary embolism (SPE) is an important differential diagnosis in patients with multiple cavitary pulmonary lesions and is most commonly associated with infective endocarditis. On imaging, SPE typically presents with peripherally distributed cavitary nodules, predominantly involving the lower lobes, often accompanied by peripheral wedge-shaped opacities;

a feeding vessel sign may also be observed [13,14]. In this case, however, the lesions were predominantly located in the upper lobes and were characterized mainly by wedge-shaped infarcted areas rather than a nodular pattern, with no feeding vessel sign identified. In addition, none of the common predisposing factors for SPE—such as intravenous drug use, indwelling vascular catheters, cardiac implantable devices, or infective endocarditis—were present. The absence of valvular vegetations or structural cardiac abnormalities on transthoracic echocardiography further reduced the likelihood of SPE. Taken together, the clinical, radiological, and echocardiographic findings support a diagnosis of septic cavitating pulmonary infarction rather than SPE.

PI may rarely lead to cavitation—either aseptic due to sterile necrosis or more commonly septic due to secondary infection [3,7]. Septic cavitation typically presents with fever, leukocytosis, and positive sputum cultures [5], as seen in this case where *Escherichia coli* was isolated from both blood and sputum. Unlike the typically solitary, large cavitary infarcts reported in literature [15], this case exhibited multiple small lesions. This was likely due to emboli involving several segmental and subsegmental arteries, creating numerous small infarcts prone to infection. Cavitation in infected emboli may occur sooner than in aseptic cases—typically around two weeks [16]. In this case, cavitation appeared within 12 days, aligning with this timeframe and supporting a diagnosis of septic pulmonary infarction.

In PI, sputum typically contains minimal bacterial or inflammatory content despite hemoptysis. However, secondary infection can mimic bacterial pneumonia [7]. In this case, positive sputum cultures confirmed infection of the infarcted tissue. This distinction is crucial, as sterile infarcts are managed with anticoagulation alone, while septic infarcts require antibiotics. This case responded well to combined anticoagulant and broad-spectrum antibiotic treatment.

PI can lead to severe complications like sepsis, empyema, pneumothorax, and bronchopulmonary fistula [17]. In cases with cavitation, surgical intervention may be recommended, especially when complications like sepsis are present [10]. However, this case showed complete clinical and radiological resolution, with only minor fibrotic changes after 8 months, indicating that medical therapy alone was sufficient.

Cavitary lung lesions are associated with a broad spectrum of infectious and non-infectious diseases and often pose significant diagnostic challenges. This case, the presence of multiple cavitary lesions initially raised suspicion for GPA. However, careful evaluation of radiological findings, absence of systemic involvement, negative microbiological and serological test results, and histopathology supported the diagnosis of infected pulmonary infarction. Although cavitation in pulmonary infarction is a recognized phenomenon, this case is distinctive because of the rapid development of multiple cavitary lesions with upper-lobe predominance and septic features, closely mimicking vasculitis and septic pulmonary embolism.The patient responded well to broad-spectrum antibiotic therapy combined with anticoagulant treatment and achieved complete clinical and radiological recovery without the need for surgical intervention. This case highlights the necessity of considering infected pulmonary infarction in the differential diagnosis of rapidly cavitating pulmonary lesions, especially in the presence of clinical signs of infection.

Informed Consent: Informed consent was not obtained because the case report contains no identifiable patient data, and the study was conducted in compliance with ethical standards for retrospective analyses.

Author contribution

Conception and design: B.S.A.; Data acquisition: B.S.A.; Data analysis: B.S.A.; Data interpretation: B.S.A.; Drafting of the manuscript: B.S.A.; Critical revision of the manuscript: B.S.A. The author reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

Written informed consent was obtained from the patient(s) or their legal guardians for the publication of this study and any accompanying images.

Data availability statement

The data supporting the findings of this study are not publicly available due to containing patient information

and are not publicly available due to privacy and ethical restrictions.

Conflict of interest

The author declares that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The author declares that during the preparation of this study, the following AI-assisted technology was used: ChatGPT-5 (OpenAI) on 15/07/2025 – 08/08/2025. Extent of Use: ChatGPT was used solely to assist with language refinement and minor phrasing adjustments in the manuscript. The author confirms that he/she has critically reviewed and edited any AI-generated content and takes full responsibility for the integrity, accuracy, and originality of the publication. The author certifies that the original human contribution is maintained and that AI-assisted tools are not listed or cited as authors..

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