

Assessment of Nicotine Addiction Risk and Challenges to Stopping Smoking among Ankylosing Spondylitis Patients

Ankilozan Spondilit Hastalarında Nikotin Bağımlılığı Riski ve Sigarayı Bırakma Zorluğunun Değerlendirilmesi

Raikan Büyükavcı ¹, Semra Aktürk ², Ümmühan Aktürk ²

1. Konya Beyhekim Training and Research Hospital, Konya

2. İnönü University, Malatya

Abstract

Objective: Smoking is a risk factor for rheumatic diseases. The objective of this study was to evaluate the relationship between high nicotine addiction risk and disease activity in patients with ankylosing spondylitis (AS) and the level of addiction risk and difficulty in quitting smoking.

Method: This was a cross-sectional study. A total of 65 patients diagnosed with AS were included in the study between November 2022 and September 2023. The following instruments were utilized: a patient identification form, the Bath Ankylosing Spondylitis Disease Activity Index, the Ankylosing Spondylitis Quality of Life Questionnaire, the Fagerström Nicotine Dependence Index, and the Challenges to Stopping Smoking.

Results: The results indicated that 36 patients (55.4%) exhibited moderate to severe nicotine addiction risk. The disease activity of 50 patients (77%) was found to be moderate to high, and these patients exhibited high smoking addiction risk scores and low quality of life scores. Among all patients, 42 (65%) expressed willingness to quit smoking, but this was significantly more challenging in those with moderate-high disease activity.

Conclusion: Smoking is one of the modifiable factors thought to influence disease activity in AS. Although quitting smoking is among the treatment recommendations in the treatment of AS, a significant portion of smokers (approximately two-thirds) are unable to quit smoking due to nicotine addiction, despite their desire to do so.

Keywords: Ankylosing spondylitis, nicotine addiction, disease activity, smoking cessation

Öz

Amaç: Sigara romatizmal hastalıklar için bir risk faktörüdür. Bu çalışmanın amacı ankilozan spondilit (AS) hastalarında yüksek nikotin bağımlılığı riski ile hastalık aktivitesi arasındaki ilişkiyi ve bağımlılık riski düzeyi ile sigarayı bırakma zorluğunu değerlendirmektir.

Yöntem: Bu çalışma kesitsel bir çalışmadır. Çalışmaya Kasım 2022 ve Eylül 2023 tarihleri arasında AS tanısı konmuş toplam 65 hasta dahil edilmiştir. Hasta tanımlama formu, Bath Ankilozan Spondilit Hastalık Aktivite İndeksi, Ankilozan Spondilit Yaşam Kalitesi Anketi, Fagerström Nikotin Bağımlılık İndeksi ve Sigarayı Bırakma Zorlukları Anketi kullanılmıştır.

Bulgular: 36 hastanın (%55,4) orta ile şiddetli nikotin bağımlılığı riski mevcuttu. Hastaların 50'sinin (%77) hastalık aktivitesinin orta -yüksek olduğu ve bu hastaların nikotin bağımlılık riski skorları yüksek ve yaşam kalitesi skorları düşük bulundu. Tüm hastalar arasında 42'si (%65) sigarayı bırakmaya istekli olduğunu ifade etti, ancak bu durum orta-yüksek hastalık aktivitesi olanlarda önemli ölçüde daha zorlayıcıydı.

Sonuç: Sigara AS' de hastalık aktivitesini etkilediği düşünülen değiştirilebilir faktörlerden biridir. Sigaranın bırakılması AS tedavisinde tedavi önerileri arasında yer alsa da, sigara içenlerin önemli bir kısmı (yaklaşık üçte ikisi) çok istemelerine rağmen yüksek nikotin bağımlılık riski nedeniyle sigarayı bırakamamaktadır.

Anahtar kelimeler: Ankilozan spondilit, nikotin bağımlılığı, hastalık aktivitesi, sigara bırakma

Introduction

Ankylosing spondylitis (AS) is the prototype of the spondyloarthropathy group of diseases and predominantly affects the axial joints and bilateral sacroiliac joints. It causes progressive limitation of spinal mobility, loss of functional ability, and decreased quality of life. The complex relationship between genetic factors and the environment is thought to be responsible for the development of all inflammatory rheumatic diseases. It is postulated that there is a complex interaction in the etiology of AS between environmental factors such as viruses, bacteria, tobacco, and genetic factors, with the HLA B27 antigen serving as a trigger for immune responses and the development of various rheumatic diseases (1).

The most recently discussed environmental factor is smoking. The impact of tobacco, a significant public health concern, on rheumatic diseases such as rheumatoid arthritis (RA), psoriatic arthritis, and systemic lupus erythematosus has been the subject of numerous investigations. The potential mechanisms by which tobacco contributes to these diverse pathologies may involve the induction of inflammation through various pathways, including the elevation of pro-inflammatory cytokines, the reduction of anti-inflammatory cytokines, the promotion of Th1 cells, and the activation of macrophages (2-4). Although there is conflicting information about the smoking rate in AS patients, a rate as high as 30% in the GESPIC cohort and 36% in the spondylarthritis group has been reported (5,6).

Although the incidence of AS is increased in smokers, studies have shown that smoking increases disease activation in patients with AS, causing more new bone formation in the spine, the most feared complication of the disease. Furthermore, this situation increases with the number of cigarettes consumed (7). Smoking can also cause structural and functional damage to the lungs, as well as serious cardiovascular risks. Given that AS itself can cause chest tightness and decreased lung capacity, it is evident that quitting smoking is of paramount importance for these patients. While both drug and non-drug treatments are recommended in the AS treatment recommendations, smoking cessation by the patient is also included (8). This is because smoking is a modifiable factor that plays a direct role in the pathogenesis of rheumatic diseases and has an indirect relationship with prognosis since the disease affects the respiratory system. Consequently, smoking cessation is a crucial step in controlling disease activity and achieving positive outcomes.

According to our hypothesis, AS patients are at high risk for nicotine addiction, which is closely related to disease activity. Furthermore, AS patients who smoke find it very difficult to quit smoking due to their high risk of nicotine addiction and chronic disease. Studies focusing on smoking cessation difficulties in people with AS are limited. In light of these predictions, we aimed to evaluate the risk of nicotine addiction, its association with disease activity, and smoking cessation difficulties in patients with AS who smoke.

Methods

Sample

A total of 65 patients diagnosed with AS who sought care at our outpatient clinic between November 2022 and September 2023 were included in the study. The study was approved by the Inonu University Scientific Research and Publication Ethics Committee (date: 11.15.2022/ number: 3957). Prior to the commencement of the study, informed consent was obtained from all participants.

A comprehensive questionnaire was then administered to obtain demographic information, including age, gender, duration of disease, accompanying comorbidities, medications used, duration and quantity of smoking, and so forth. Patients with a history of additional psychiatric illness and/or related medication use were excluded from the study.

Power analysis was performed with the G*Power statistical program (ver.3.1.9.7). When Cohen's d effect size of 0.5 (medium), type I error rate of $\alpha=0.05$ and power $1-\text{Beta}=0.80$ were considered, it was calculated that 64 patients were required.

Measures

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

This is a scale that includes questions to assess fatigue, spinal or peripheral joint pain, local tenderness, qualitative and quantitative morning stiffness in AS patients, and has a 10 cm visual analog scale (VAS). The patients are asked to score the questions from easy to difficult on a scale of 0 to 10. Finally, a total score is calculated for each patient. Chronbach's alpha had a satisfactory value of 0.80 (9). In the present study, BASDAI scores below 4 were considered indicative of low disease activity, while scores of 4 and above were considered indicative of moderate to high disease activity (10).

Bath Ankylosing Spondylitis Functional Index (BASFI)

It is a 10-item self-administered questionnaire designed to assess the function and activities of daily living in patients with ankylosing spondylitis. The total scores on the test range from 0 to 10, with higher total scores being indicative of a worse functional status. A Turkish validity and reliability study of the scale was conducted. Reliability analysis showed a Cronbach's alpha score of 0.926 (11).

AS-specific Quality of Life (ASQoL)

This scale is developed to assess the quality of life of patients in the ED, is a valid and reliable tool that can be used in both clinical practice and scientific research. The items in this survey are an 18-item scale that includes phrases commonly used by patients with AS. 7 of the items in the test include evaluations of the patient's daily activities, 7 of them about their mental state, 2 of them about the intensity of the pain they feel, and 2 of them about their social life. When scoring the scale, it is assumed that as the total score increases, the individual's quality of life deteriorates. Duruöz MT et al. published the reliability and validity of ASQoL in Turkish was published as a summary of the paper by (12).

Fagerstrom Nicotine Dependency Index (FNDI)

In a study conducted in Turkey, the reliability of the Fagerstrom Test for Nicotine Dependence was found to be moderate and it was concluded that it could be applied in smoking cessation clinics in Turkey (13). The content of this test examines the amount of cigarettes smoked by the person and the degree of being able to stop smoking for a certain period. The questionnaire consists of 6 questions and the score varies between 0 and 10. As the score increases, it is thought that smoking addiction increases.

The Challenges to Stopping Smoking (CSS-21)

This scale has a total of two subscales: 9 items relate to the personal aspect of quitting, and 12 items relate to the social or environmental aspects. It consists of 21 items scored out of 4 points. The higher the score, the harder it is to quit smoking. Its Turkish validity and reliability were tested (14).

Statistical Analysis

The following statistical data were collected: The sociodemographic data of the patients who participated in the study and the data from the survey forms used were transferred to the statistical program SPSS (Statistical Package for Social Sciences, version 22.0) for analysis. Descriptive statistics were expressed as the mean and standard deviation for continuous variables and as numbers and percentages for categorical variables. Kolmogorov-Smirnov analysis was used for normality and reliability analysis. Independent sample t-tests were applied for two-group comparisons using parametric tests. Pearson correlation analysis was used for relational analyses. The statistical significance level was set at $p < 0.05$.

Results

The mean age of the patients was 45.8 ± 4.7 years, and the mean disease duration was 8.8 ± 4.2 years. 44.6% of patients had at least one additional chronic disease. BASDAI and BASFI mean scores were moderate-high (respectively: 4.6 ± 1.3 and 4.4 ± 1.7). Biologic agents were used in more than half of the

patients. The average number of cigarettes smoked per day and the duration of smoking were also quite long. Table 1 presents the demographic data and disease activity scores of the patients.

Table 1: Main characteristics of patients

Variable	Mean±SD / n (%)
Age (years±SS)	45.8±4.7
Male gender (n%)	52 (80)
Comorbidities (n%)	29 (44.6)
Disease duration (years±SS)	8.8±4.2
Marital status (n%)	
Married	54 (83.1)
Single	6 (9.2)
Widowed	5 (7.7)
Education status (n%)	
Illiterate	6 (9.2)
Primary school	25 (38.4)
High school	22 (34)
University	12 (18.4)
BASDAI disease activity score (n/%)	
<4 Mild disease activity	15 (23)
≥4 Moderate to high disease activity	50 (67)
BASDAI scores	4.6±1.3
BASFI scores	4.4±1.7
ASQoL scores	9±3.4
Medications (n%)	
NSAID	16 (24.6)
DMARD	10 (15.3)
Biological agents	58 (89.2)
Cigarette smoking	
Per day	18 (5-60)
Package/year	17.9±9
Fagerstrom nicotine dependence index (FNDI) (n%)	
Very mild dependence (0-2 points)	9 (13.8)
Mild dependence (3-4 points)	20 (30.8)
Moderate dependency (5 points)	8 (12.3)
Severe dependency (6-7 points)	20 (30.8)
Very severe dependency (8-10 points)	8 (12.3)
The Challenges to Stopping Smoking (CSS-21) Scale (n%)	42 (64.6)
CSS-21 score (21-84 puan)	45.6±12.5

BMI: Body mass index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: The Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of life; NSAID: Non-steroidal anti-inflammatory drugs; DMARD: Disease Modifying Anti-Rheumatic Drugs

According to BASDAI scores, the disease activity of 50 patients (77%) was determined to be moderate-high. In these patients, nicotine addiction risk scores were high, and quality of life scores were low ($p < 0.001$) (Table 2).

Among all patients, 42 patients (65%) expressed a willingness to quit smoking. However, this was significantly more challenging for those with moderate-to-high disease activity ($p = 0.001$).

Table 2: Comparison of functional status, quality of life, and nicotine dependence levels of patients according to disease activity scores

	BASDAI Mild disease activity (n:15) Mean±SD	BASDAI Moderate to high disease activity (n:50) Mean±SD	p-value
BASFI	2.8±0.8	4.9±1.6	<0.001*
ASQoL	5.8±1.7	10.0±3.7	<0.001*
FNDI	3.6±0.8	5.3±2.1	0.003*

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: The Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of life; FNDI: Fagerstrom Nicotine Dependence Index; p value: * independent t-test

Disease activity scores (BASFI and BASDAI) were positively correlated with the nicotine dependence index and CCS-21 scores ($p < 0.05$) (Table 3).

Table 3. Pearson correlation analysis on the relationship between disease activity scores and FNDI and CCS-21

	FNDI	CCS-21
BASDAI		
p	0.03	<0.001
r	.261	.614
BASFI		
p	0.039	0.006
r	.256	.421

The correlation is significant at the 0.05 level; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: The Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of life; FNDI: Fagerstrom Nicotine Dependence Index.

Discussion

The findings of this study indicate that smoking in AS patients is associated with higher disease activity, decreased function, and quality of life. Concurrently, nicotine addiction risk and the difficulty of quitting are both high among this patient population. The relationship between smoking and rheumatoid arthritis (RA), one of the inflammatory diseases, was first demonstrated in the scientific literature. It was reported that smoking is the strongest known environmental risk factor for the development of RA (15). Videm V et al. demonstrated that current smoking was significantly associated with RA (16).

In a study of patients with early axial spondyloarthritis (AxSpA), smoking was found to be independently associated with an earlier onset of inflammatory low back pain, higher disease activity, increased axial structural damage, worse functional status, and worse quality of life (17). In a systematic review, although the level of evidence was limited, it was found that patients with AS who smoked were more severely affected than non-smokers in terms of pain, general health assessment, disease activity, physical mobility, and quality of life (18). A recent study, which included data from our country, found that AS patients who smoked exhibited higher initial disease activity, functional disability, and impaired quality of life compared to non-smokers (19). The impact of smoking on the response to tumor necrosis factor inhibitors (TNFi), a class of drugs that have been extensively utilized in the treatment of AS in recent years and have high remission rates, has also been the subject of studies. A systematic review revealed a paucity of scientific evidence regarding the association between smoking habits and treatment response in axial spondyloarthritis (AxSpA) (20).

A recent large study demonstrated that smoking did not affect initial TNF- α inhibitor responses, although baseline disease activity was higher in AS patients who smoked than in non-smokers (19). In our study, the disease duration of the patients with AS who were followed up was considerable, and the majority of them were undergoing treatment with TNFi. Nevertheless, their disease activity was high, their functional capacity was limited, and their quality of life scores were low. Although this situation cannot be directly attributed to smoking, it does suggest the existence of an indirect relationship, as evidenced by the statistically higher nicotine dependence index observed in our patients with high disease activity. The study did not include non-smoking patients and did not include radiographic evaluation of patients.

The existing literature on smoking dependence in AS patients is limited. One study has demonstrated that sexual function in AS patients is associated with cumulative smoking exposure, independent of other disease-related factors. Furthermore, sexual function tends to decrease with increasing smoking dependence. In addition to the direct effect of smoking on erectile dysfunction, this study found that BASMI scores were higher in those with a higher degree of nicotine dependence, as was observed in our previous study. In the patient cohort under investigation, 55.4% exhibited moderate to severe nicotine dependence, as determined by the Addiction Index. This rate was comparable to that observed in the study by Aykurt Karlıbel *et al* (21). On the other hand, disease activity scores were positively correlated with nicotine dependence; and smoking cessation scores in patients who wanted to quit smoking.

Smoking cessation is one of the European League Against Rheumatism (EULAR) recommendations for cardiovascular risk management in patients with inflammatory arthritis (8). A study was conducted in a rheumatology clinic to evaluate the efficacy of a smoking cessation program for patients with rheumatic diseases (22). A subsequent study demonstrated that brief counseling was more effective than no counseling in promoting smoking cessation (23). A recent study conducted in our country revealed that a significant proportion of patients with AS were not assessed for smoking during routine follow-up (24). Conversely, it has been observed that the factor that has the greatest impact on smokers is the recommendation of a rheumatologist. Consequently, it is imperative that the issue of smoking addiction in AS patients be addressed and that smoking cessation recommendations be emphasized by the treating physician. In our study, two-thirds of the patients expressed a desire to quit smoking. Nevertheless, no suggestions or initiatives were made in this direction. Alternatively, we did not inquire about the patients' unsuccessful attempts to quit smoking.

The principal limitations of this study are the modest sample size and the fact that it included only smokers. Another important limitation of our study is that it is a cross-sectional study; cause and effect relationship cannot be established and temporal differences may develop. Moreover, large-scale prospective studies must be conducted to investigate smoking dependence and smoking cessation strategies.

In conclusion, smoking is regarded as one of the most significant preventable factors influencing disease activity in AS, an inflammatory rheumatologic disease that is more prevalent in males. Although smoking cessation is one of the recommended treatments for AS, a significant proportion of smokers (approximately two-thirds) are unable to quit smoking due to nicotine addiction, despite their desire to do so. It is recommended that physicians caring for patients with AS assess their smoking habits, addiction, and cessation recommendations during routine follow-up. It has been shown that even recommending the patient to quit smoking is more effective than not recommending smoking at all (25). To increase success in the fight against smoking, especially among individuals with chronic smoking-related diseases, all community health care providers should be made aware that they should ask every patient if they smoke. If they do, they should be encouraged to quit and directed to a cessation program (26).

References

1. Chen CH, Chen HA, Lu CL, *et al*. Association of cigarette smoking with Chinese ankylosing spondylitis patients in Taiwan: a poor disease outcome in systemic inflammation, functional ability, and physical mobility. *Clin Rheumatol* 2013; 32(5): 659-663.

2. Stolt P, Bengtsson C, Nordmark B, et al. EIRA study group. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population-based case-control study, using incident cases. *Ann Rheum Dis* 2003; 62(9): 835-841.
3. Criswell LA, Merlino LA, Cerhan JR, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. *Am J Med* 2002; 112(6): 465-471.
4. Costenbader KH, Kim DJ, Peerzada J, et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. *Arthritis Rheum* 2004; 50(3): 849-857.
5. Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis Rheum* 2012; 64: 1388-1398.
6. Kaut IK, Abourazzak FE, Jamila E, et al. Axial spondyloarthritis and cigarette smoking. *The Open Rheumatology J* 2017; 11: 53-61.
7. Akar S, Kaplan YC, Ecemiş S, et al. The role of smoking in the development and progression of structural damage in axial SpA patients: A systematic review and meta-analysis. *Eur J Rheumatol* 2019; 6(4): 184-192.
8. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; 69: 325-331.
9. Akkoç Y, Karatepe AG, Kirazlı Y, et al. Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index: reliability and validity. *Rheumatol Int* 2005; 25(4): 280-284.
10. Mısırcı S, Alp A, Altan L, Yılmaz BB. Systemic immune inflammation index in ankylosing spondylitis patients. *Turk J Osteoporos* 2024; 30(1): 22-29.
11. Özer HT, Sarpel T, Gulek B, et al. The Turkish version of the Bath Ankylosing Spondylitis Functional Index: reliability and validity. *Clin Rheumatol* 2005; 24(2): 123-128.
12. Duruöz MT, Doward L, Turan Y, et al. Translation and validation of the Turkish version of the Ankylosing Spondylitis Quality of Life (ASQOL) questionnaire. *Rheumatol Int* 2013; 33(11): 2717-2722.
13. Uysal MA, Kadakal F, Karşıdağ C, et al. Fagerström test for nicotine dependence: reliability in a Turkish sample and factor analysis. *Tuberk Toraks* 2004; 52: 115-121.
14. Can-Gür G. Psychometric properties of the Turkish version: The Challenges to Stopping Smoking (CSS-21) Scale. *J Subst Use* 2021; 26(1): 107-113.
15. Sugiyama D, Nishimura K, Tamaki K, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2010; 69(1): 70-81.
16. Videm V, Cortes A, Thomas R, Brown MA. Current smoking is associated with incident ankylosing spondylitis : The HUNT Population-based Norwegian Health Study. *J Rheumatol* 2014; 41(10): 2041-2048.
17. Chung HY, Machado P, van der Heijde D, et al. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIRE cohort. *Ann Rheum Dis* 2012; 71(6): 809-816.
18. Villaverde-García V, Cobo-Ibáñez T, Candelas-Rodríguez G, et al. The effect of smoking on clinical and structural damage in patients with axial spondyloarthritis: A systematic literature review. *Semin Arthritis Rheum* 2017; 46(5): 569-583.
19. Tuğsal HY, Artin GK, Can G, et al. The impact of smoking on response to tumor necrosis factor- α inhibitor treatment in patients with ankylosing spondylitis. *Turk J Med Sci* 2023; 53(4): 970-978.
20. Zurita Prada PA, Urrego Laurín CL, Guillén Astete CA, et al. Influence of smoking and obesity on treatment response in patients with axial spondyloarthritis: a systematic literature review. *Clin Rheumatol* 2021; 40(5): 1673-1686.
21. Aykurt Karlıbel İ, Dülger S, Kasapoğlu Aksoy M, et al. Effect of cigarette smoking on sexual functions, psychological factors, and disease activity in male patients with ankylosing spondylitis. *Aging Male* 2019; 22(2): 109-115.
22. Naranjo A, Bilbao A, Erausquin C, et al. Results of a specific smoking cessation program for patients with arthritis in a rheumatology clinic. *Rheum Int* 2014; 34(1) : 93-99.
23. Stead LF, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2013; (5): CD000165.
24. Kaya MN, Yurumez S, Tekgöz E, et al. The role of rheumatologist in smoking cessation of ankylosing spondylitis patients: a single-center cross-sectional study. *Cureus* 2023; 15(9): e45461.
25. Slama K, Redman S, Perkins J, Reid AL, Sanson-Fisher RW. The effectiveness of two smoking cessation programs for use in general practice. A randomized clinical trial. *BMJ* 1990; 300: 1707-9.
26. Bozkurt N, Bozkurt Aİ, Erdoğan A. What is the most important problem in smoking cessation? *Akdeniz Medical Journal* 2020; 6(3): 430-438.

Yazar Katkıları: Tüm yazarlar ICMJE'in bir yazarda bulunmasını önerdiği tüm ölçütleri karşılamışlardır

Etik Onay: Bu çalışma için ilgili Etik Kuruldan etik onay alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir

Not: Bu makalenin içeriği 4. Uluslararası TURAZ kongresinde sözlü bildirisi olarak sunulmuştur.

Author Contributions: All authors met criteria recommended by ICMJE for being an author

Ethical Approval: Ethical approval was obtained for this study from relevant Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have declared that there is no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Acknowledgement: The content of this article was presented as an oral presentation at the 4th International TURAZ Congress.