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Epicardial Adipose Tissue Thickness and Related Factors in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Epikardial Adipoz Doku Kalınlığı ve İlişkili Faktörler

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Abstract

Objective: This study aimed to investigate epicardial adipose tissue thickness (EATT) and related factors in patients with ankylosing spondylitis (AS) and to compare the results with those of healthy controls.

Materials and Methods: This cross-sectional study included 30 patients diagnosed with AS based on the modified New York criteria. The control group consisted of 31 healthy volunteers. Demographic characteristics were recorded, and EATT was measured by transthoracic echocardiography. The Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), Bath AS Metrology Index (BASMI), AS Disease Activity Score (ASDAS), AS Quality of Life (ASQoL), and International Physical Activity Questionnaire Short Form were used. Functional capacity was assessed using the six-minute walk test (6-MWT).

Results: The mean age was 41.67±7.56, and 21 (70%) participants were male in the AS group. The mean disease duration was 10.0 (standard deviation ±7.2) years in the AS group. The mean EATT values were 4.40±1.65 mm and 2.85±1.12 mm in the AS and control groups, respectively (p<0.001). A notable negative correlation was observed between EATT and erythrocyte sedimentation rate (ESR) (p<0.05). Significant positive correlations were also observed between EATT and body mass index (BMI), BASFI, and BASMI. Additionally, EATT was linearly associated with the severity of sacroiliitis (r=0.400, p=0.028). There were no significant correlations between EATT and disease duration, C-reactive protein levels, blood lipid levels, ASDAS, ASQoL, IPAQ, and 6-MWT (p>0.05).

Conclusion: EATT values were higher in patients with AS than in those without AS. The factors related to EATT were BMI, ESR, BASFI, BASMI, and the severity of sacroiliitis.

Keywords: Ankylosing spondylitis, atherosclerosis, epicardial adipose tissue thickness, body mass index, sacroiliitis

Öz

Amaç: Bu çalışmanın amacı, ankilozan spondilit (AS) hastalarında epikardiyal adipoz doku kalınlığı (EATT) ve ilişkili faktörleri incelemek ve elde edilen sonuçları sağlıklı kontrol grubunun bulguları ile karşılaştırmaktır.

Gereç ve Yöntem: Bu kesitsel çalışma, modifiye New York kriterlerine dayanarak AS tanısı almış olan 30 hastayı içermektedir. Kontrol grubu ise 31 sağlıklı gönüllüden oluşmaktadır. Çalışma başlangıcında demografik özellikler kaydedildi. EATT transtorasik ekokardiyografi ile ölçüldü. Bath AS Hastalık Aktivite İndeksi (BASDAI), Bath AS Fonksiyonel İndeksi (BASFI), Bath AS Metroloji İndeksi (BASMI), AS Hastalık Aktivite Skoru (ASDAS), AS Yaşam Kalitesi (ASQoL), Uluslararası Fiziksel Aktivite Anketi Kısa Formu kullanıldı. Fonksiyonel kapasitenin değerlendirilmesi ise altı dakikalık yürüme testi (6-MWT) kullanılarak gerçekleştirildi.

Bulgular: AS grubunda ortalama yaş 41,67±7,56 idi ve bu grupta 21 kişi (%70) erkekti. Ortalama EATT değerleri sırasıyla AS ve kontrol gruplarında 4,40±1,65 mm ve 2,85±1,12 mm idi (p<0,001). EATT ile eritrosit sedimantasyon hızı (ESR) arasında anlamlı bir negatif korelasyon bulundu (p<0,05). EATT ile vücut kitle indeksi (VKİ), BASFI ve BASMI arasında istatistiksel olarak anlamlı pozitif korelasyon mevcuttu. EATT ve sakroileit derecesi arasında lineer bir korelasyon vardı (r=0,400, p=0,028). EATT ile hastalık süresi, C-reaktif protein, kan lipitleri, ASDAS, ASQoL, IPAQ ve 6-MWT arasında anlamlı korelasyon saptanmadı (p>0,05).

Sonuç: Bu çalışmada, EATT değerlerinin AS hastalarında kontrol grubuna göre daha yüksek olduğunu bulunmuştur. EATT ile ilişkili faktörler VKİ, ESR, BASFI, BASMI ve sakroileitin şiddeti olarak belirlendi.

Anahtar kelimeler: Ankilozan spondilit, ateroskleroz, epikardial adipoz doku kalınlığı, vücut kitle indeksi, sakroileit

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Introduction

Ankylosing spondylitis (AS) is a long-term systemic inflammatory disease that primarily involves the spinal column and sacroiliac joints and is often linked to extra-articular manifestations (1). Individuals with AS often display features of metabolic syndrome, such as obesity, elevated blood pressure, abnormal lipid levels, insulin resistance, and disrupted glucose metabolism (2). In addition to these traditional vascular risk factors, chronic inflammation is also linked to an elevated risk of atherosclerosis in patients with AS. The prevalence of atherosclerosis is 1.5 times higher in AS than in healthy individuals. Cardiac involvement is seen in 10-30% of patients with AS (3).

Atherosclerosis involves a prolonged inflammatory response in the vascular wall, resulting in the gradual formation of multifocal plaques within arteries. Persistent inflammation is widely recognized as a standalone risk factor contributing to the advancement of atherosclerosis. Proinflammatory alterations in epicardial adipose tissue (EAT) could be pivotal in the progression of coronary atherosclerosis (4). EAT refers to the layer of superficial fat located on the myocardium's surface. Compared to other adipose tissues, increased inflammatory responses in EAT are a stronger marker of coronary artery disease (4).

Atherosclerosis is believed to contribute notably to mortality in AS patients. Cardiac involvement tends to be more prevalent among those with a longer disease duration (3). Rheumatologists must be aware of cardiovascular involvement signs in AS patients and regularly monitor them for cardiac issues (5). Recognition of subclinical atherosclerosis in asymptomatic patients is important for prevention. EAT, which can be used as an indicator of subclinical atherosclerosis, is now more frequently studied in AS patients. EAT, located around the heart and coronary arteries, functions in both endocrine and paracrine capacities as a form of visceral fat. It is proposed that EAT may impact the progression of coronary atherosclerosis through the release of various pro-inflammatory and anti-inflammatory cytokines and chemokines. (6).

Measurement of EAT thickness (EATT) using echocardiography has the potential to reveal early signs of atherosclerosis in AS patients. Studies have reported increased EATT levels in patients with AS when compared to those in the healthy control group (7, 8). Moreover, chronicity of the disease, body mass index (BMI), inflammatory markers, lipid profile, Bath AS Functional Index (BASFI) (9), and Bath AS Disease Activity Index (BASDAI) (10) have been suggested as factors related to EATT. Despite the long-standing initial findings suggesting that EATT could be a marker of atherosclerosis and cardiovascular risk in AS patients, there are still limited studies on this topic in the literature (7).

This study set out to examine EATT and its related factors in patients with AS, with comparisons made to a healthy control group. Additionally, while previous research typically examined the correlation between EATT and clinical and blood parameters that indicate disease activity (7,8), this study is novel in examining the relationship between EATT and the severity of sacroiliitis, as well as physical activity levels evaluated by The International Physical Activity Questionnaire Short Form (IPAQ-SF) and the 6-minute walk test (6-MWT).

Materials and Methods

Participants

The study was designed as a cross-sectional clinical study. The medical records of 240 patients with AS in the Istanbul Physical Medicine Rehabilitation Training and Research Hospital outpatient clinic were screened between August 2015 and January 2016. The inclusion criteria were a disease duration of more than one year, being 18 years or older, and having a diagnosis of AS according to the modified New York Criteria (11). The exclusion criteria included illiteracy, being over 65 years old, and having a history of ischemic heart disease, hypertension, chronic kidney failure, or endocrinopathies such as diabetes mellitus, hypothyroidism, cerebrovascular disease, Cushing's syndrome, and primary hyperlipidemia. A total of 200 subjects were excluded due to the above-mentioned exclusion criteria. Out of the remaining 40 patients, 10 chose not to participate in the study. Therefore, 30 patients were included, and the control group consisted of 31 age-matched healthy volunteers. The estimated sample size was 22 participants for each group (12).

Ethics

Ethical approval was granted by the Local Ethics Committee of Bakırköy Dr. Sadi Konuk Education and Research Hospital and subsequently approved by the Turkish Ministry of Health (decision no: 2016/03/10, date: 11.04.2016). Informed consent, both oral and written, was obtained from each patient before their participation in the study.

Demographics and Measurements

Demographic features, including age, gender, body weight, and height, were documented. BMI was calculated (kg/m^2). The duration of disease, smoking history, and any additional illnesses were also noted. All patients underwent a physical examination. Serum fasting blood sugar, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) values were obtained from the patients' follow-up records within the last month. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were also recorded. Very LDL-C (VLDL) levels were calculated using the Friedewald formula. Standard anteroposterior pelvic roentgenograms from the patients' follow-up records in the past month were reviewed by the same physiatrist. Sacroiliitis was graded according to the New York Criteria (11). The BASDAI was used to assess disease activity (10), while the Bath AS Metrology Index (BASMI) measured activity limitation (13). BASFI was utilized to evaluate functional status (9), and quality of life was assessed using the AS Quality of Life (ASQoL) questionnaire (14). Additionally, the AS Disease Activity Score with CRP (ASDAS-CRP) (15) was used alongside BASDAI to assess disease activity.

IPAQ-SF (16) was employed to evaluate physical activity levels over the previous 7 days. IPAQ helps measure physical activity in AS patients (16). The 6-MWT was performed by walking a 30-meter flat path marked with return points. Both pretest and posttest heart rate, blood pressure, oxygen saturation levels, and walking distance were recorded. The 6-MWT serves as a prognostic and predictive measure for cardiovascular disease and can also be used to assess function in patients with AS (17). All assessments were conducted by the same physiatrist.

Transthoracic echocardiography [Vivid 7 Dimension by GE Vingmed Ultrasound, located in Horten, Norway (Model N-3190)] using a 2.5 MHz probe was performed to examine the heart in all participants. EATT was measured using parasternal long axis images obtained from the right ventricular free wall at the end of systole while the patients were positioned in the left lateral decubitus position (18). The average of three measurements was calculated. All echocardiograms were conducted by the same cardiologist.

Statistical Analysis

Data analysis was performed with IBM SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics [mean, standard deviation (SD), median (minimum-maximum), frequency, and percentage] were utilized. The distribution of variables was evaluated using the Kolmogorov-Smirnov test, revealing a deviation from normality. Consequently, non-parametric tests were applied. The Mann-Whitney U test was applied for analyzing quantitative data, and Spearman correlation analysis was conducted to assess relationships. Statistical significance was set at p-values less than 0.05. Sample size estimation was performed using MedCalc Statistical Software. The estimation was based on EATT values, anticipating a group difference of more than 1.04 mm, with a false-positive rate of 5% (α= 0.05) and a minimum power of 80% (β= 0.20), as described in Ustun et al. study (12).

Results

Demographic characteristics and EATT values are shown in Table 1. No significant differences were found regarding age, gender,

Table 1. Demographic variables and EATT

Variable	AS	Healthy controls	p-value
	n=30	n=31	
Mean age (years)	41.67±7.56	44.10±14.90	0.799
Gender (male, %)	70 % (n=21)	45.2 % (n=14)	0.088
Smoking	33% (n=10)	25.8% (n=8)	0.13
Body mass index, kg/m^2	26,58±4.33	25.6±4.5	0.7
Mean EATT, mm	4.40±1.65	2.85±1.12	<0.001

EATT: Epicardial adipose tissue thickness, AS: Ankylosing spondylitis

smoking status, and BMI between the patients and the control group. The mean EATT value was statistically significantly higher in the AS group (p<0.001). The mean disease duration in the AS group was 10.0 SD± 7.2) years. Eleven patients (36.7%) had comorbidities, and almost one-third were smokers. Nine patients (30%) were using nonsteroidal anti-inflammatory drugs, 4 (13.3%) were taking sulfasalazine, and 21 (70%) were using anti-tumor necrosis factor (TNF) therapy.

Demographic and clinical features in AS patients, along with correlations between EATT, are shown in Table 2. Statistically significant positive correlations were found between EATT and BMI, BASFI, and BASMI (p<0.05) (Table 3). There was a significant negative correlation between EATT and ESR (p=0.037). No significant correlations were found between EATT and disease duration, ASDAS, ASQoL, CRP, blood lipids, 6-MWT, or IPAQ (p>0.05) (Table 2).

Clinical characteristics were compared based on gender and are summarized in Table 3. BASFI, BASMI, and EATT were significantly higher in men compared to women (p<0.05). However, no significant differences were observed between the sexes with respect to ASDAS, BASDAI, ASQoL, IPAQ, and 6-MWT (p>0.05) (Table 3).

According to the New York criteria, sacroiliitis was graded on standard anteroposterior pelvic roentgenograms as follows: one patient (3.3%) had Grade 1, five patients (16.7%) had Grade 2, twelve patients (40%) had Grade 3, and twelve patients (40%) had Grade 4 sacroiliitis. A linear correlation was found between EATT and the grade of sacroiliitis (F= 5.344, p= 0.028 regression analysis; correlation r= 0.400, p= 0.028) (Figure 1).

Discussion

In this investigation, the mean EATT value demonstrated a significant elevation within the AS group, corroborating findings from previous research that similarly reported elevated EATT values among AS patients. This consistency lends further credence to our own results. Moreover, our study revealed a positive correlation between EATT and BMI, BASFI, and BASMI, while a negative correlation was observed between EATT and ESR. Additionally, we identified a linear correlation between EATT and the severity of sacroiliitis (7).

Previous studies have implicated various factors such as disease duration, BMI, inflammatory markers, lipid profile, BASFI, and BASDAI in relation to EATT. Notably, our study uncovered a negative correlation between EATT and disease activity, as indicated by ESR levels, although no significant correlation was found with CRP in our cohort. The literature regarding the association between atherosclerosis and disease activity in AS patients presents conflicting findings. Some studies have reported a positive correlation (19) between carotid intima-media thickness (CIMT) and ESR in AS patients, while other studies found no correlation (7). Conversely, a negative correlation between CIMT and ESR has been reported previously (20, 21). Additionally, some studies revealed no significant correlations between CRP and CIMT (20, 22). In our study, we observed a significant negative correlation between EATT and ESR, a laboratory marker of disease activity. This result is consistent with previous studies (20). However, as ESR reflects the present status of disease activity, it may not accurately represent the overall inflammatory burden of the disease. Disease activity markers often reflect recent inflammation levels but may not capture the cumulative level of inflammation over time.

In this study, EATT was significantly related to BMI; however, previous studies have not reported significant cholesterol (TC), between EATT and BMI in AS patients (7, 8). There were no significant correlations between EATT and total cholesterol(TC), TG, LDL-C, or HDL-C levels in our study. Surucu et al. (8) reported negative correlations between EATT and either TC or LDL cholesterol in patients with AS. Tekaya et al. (23) and Resorlu et al. (7) reported that EATT was significantly correlated with TG, but there were no significant correlations between EATT and

Table 2. Correlations with EATT in patients with AS

Variables of AS patients	Mean±SD	EATT r	p-value
Age (years)	41.67±7.56	0.334	0.07
Disease duration (years)	10.03±7.19	0.03	0.791
Weight (kg)	76.87±16.50	0.383	**0.037**
BMI (kg/m^2)	26.58±4.33	0.428	**0.018**
BASDAI	3.73±1.78	0.036	0.811
BASFI	3.39±2.39	0.475	**0.008**
BASMI	4.64±2.19	0.359	**0.05**
ASDAS	2.46±1.01	0.165	0.384
ASQOL	6.23±4.81	0.174	0.357
C-reactive protein (mg/dL)	7.34±8.12	0.218	0.248
Erythrocyte sedimentation rate (mm/h)	15.73±15.54	-0.382	**0.037**
Total cholesterol (mg/dL)	193.43±39.68	-0.111	0.559
LDL cholesterol (mg/dL)	117.57±29.95	-0.048	0.801
HDL cholesterol (mg/dL)	47.13±10.44	-0.125	0.510
Tryglyceride (mg/dL)	193.43±71.94	0.004	0.982
Atoregenic Index (Log 10TG/HDL)	0.42±0.24	0.089	0.640
6-minute walking (m)	433.33±63.04	-0.0159	0.402
IPAQ (MET-min/wk.)	1832.16±2822.92	0.265	0.158
EATT (cm)	0.44±0.16	1	

BASDAI: The Bath AS Disease Activity Index, BASMI: the Bath Ankylosing Spondylitis Metrology Index, BASFI: The Bath AS Functional Index, BMI: Body-mass index, ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire, ASDAS: AS Disease Activity Score, IPAQ: The International Physical Activity Questionnaire, MET: The metabolic Equivalent, EATT: Epicardial adipose tissue thickness, Spearman correlation

Table 3. Relationship between clinic varriables and gender

Variables of AS patients	Male n=21		Female n=9		p-value
	Mean±SD	**Median**	**Mean±SD**	**Median**	
Age (years)	42.24±6.572		40.33±9.823		**<0.001**
ASDAS	2.6±1.1	2.4	2.1±0.8	2.0	0.213
BASDAI	3.8±2.0	4.3	3. 6±1.3	3.4	0.786
BASFI	4±2.5	3.6	2.0±1.4	1.8	**0.030**
BASMI	5.2±2.3	5.6	3.3±1.1	3.2	**0.030**
ASQOL	6.8±5.4	5.0	5.0±2.7	5.0	0.699
IPAQ (MET-min/wk.)	2080±3138	693	1253±1931	537	0.415
EATT (cm)	0.5±0.1	0.5	0.3±0.1	0.3	**<0.001**
6-minute walking (m)	432±68	450.0	436.7±52.3	450	0.927

ASDAS: AS Disease Activity Score, BASDAI: The Bath AS Disease Activity Index, BASFI: The Bath AS Functional Index, BASMI: The Bath Ankylosing Spondylitis Metrology Index, ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire, IPAQ: The International Physical Activity Questionnaire, MET: The metabolic Equivalent, EATT: Epicardial adipose tissue thickness. Mann-whitney u test either LDL-C or HDL-C in patients with AS. Iacobellis et al. found a significant correlation between EATT and LDL-C, adiponectin, and arterial blood pressure (24). However, a previous study reported no significant correlations between CIMT and blood lipids in AS (21). Considering other studies (7, 8, 21) and our results, which did not find significant correlations between lipid levels and EATT, the exclusion of patients with atherosclerotic risk factors at the beginning of the study may explain this common finding. On the other hand, in the study by Iacobellis et al. (24), individuals with coronary artery disease were included, which makes their results inconsistent with our study. This finding supports the idea that the increase in EATT is secondary to AS pathogenesis and independent of the lipid profile.

EATT exhibited a positive correlation with both BASFI and BASMI in our study. However, no significant correlations were observed between EATT and ASDAS, BASDAI, or ASQoL. Previous research has reported significant correlations between BASFI and either EATT or CIMT, which is consistent with our findings (8, 20). However, some studies did not find significant correlations between EATT and either BASDAI or BASFI (7, 12). Similarly, Gupta et al. (21) reported no correlations between CIMT and either BASDAI or BASFI, but noted a significant positive correlation between CIMT and BASMI in the same study. These conflicting results may be attributed to the differing sensitivities of disease activity measures. BASDAI and ASDAS primarily reflect recent disease activity, while metrological and functional indices provide more objective indicators of disease progression and damage.

In this investigation, BASFI and BASMI scores were significantly higher in men compared to women. This finding aligns with a study conducted by Shahlaee et al.(25), which also reported significantly higher BASMI scores in male AS patients. Furthermore, our study revealed that EATT was significantly higher in men than in women. This observation may be explained by the widely recognized fact that male gender is a risk factor for coronary artery disease at younger ages, providing a plausible rationale for our findings (26).

In this study, we did not observe a significant correlation between EATT values and the 6-MWT. The 6-MWT is an important measure for assessing the functional capacity of patients with cardiac diseases (27). Carvalho et al. (28) reported a correlation between the 6-MWT and cardiopulmonary test in patients with heart failure. Given that the 6-MWT was found to be practical, well-tolerated, and cost-effective, it is proposed as a suitable alternative to cardiopulmonary testing. To our knowledge, no studies have yet investigated the association between the 6-MWT and subclinical atherosclerosis in AS patients. However, studies with larger sample sizes are needed to draw definitive conclusions about this correlation.

Similarly, no correlation was observed between EATT and IPAQ in this study. Notably, we did not identify any studies exploring the correlation between the IPAQ-Short Form and EATT. In line with this, a prior study found no significant correlations between EATT and either disease activity or the functional status of patients (29). Tekaya et al. (30) found that radiographic structural damage was a predictor of increased EATT in spondyloarthritis. While previous studies have explored the relationship between disease activity and EATT (7, 8), few have compared radiographic findings with EATT. In our study, a correlation was found between EATT and the grade of sacroiliitis. Sacroiliitis, a hallmark of AS, represents ongoing local inflammation in the sacroiliac joints (31). It is well-known that chronic inflammation in AS affects not only the joints but also other tissues, including cardiovascular structures. EAT is recognized as a highly inflammatory fat depot, capable of secreting pro-inflammatory cytokines such as interleukin-6 and TNF-α, which are central to the pathophysiology of AS (32). These cytokines may contribute to both joint and cardiovascular inflammation, providing a potential link between sacroiliitis and increased EATT (31, 32).

Additionally, the severity of sacroiliitis may reflect a higher overall inflammatory burden in AS, which could contribute to subclinical atherosclerosis, as indicated by increased EATT. The chronic inflammatory state in AS may promote adipose tissue dysfunction, leading to ectopic fat deposition, including in the epicardial region (32, 33). This inflammatory process could explain why patients with more severe sacroiliitis tend to have higher EATT values. Further studies are needed to clarify whether controlling sacroiliitis through treatment could also reduce cardiovascular risk, as reflected by changes in EATT.

Study Limitations

There are several strong points and some limitations in this study. This study is limited by its relatively small sample size and absence of a follow-up period, which may affect the robustness of the findings. It is important to acknowledge that magnetic resonance imaging (MRI) is currently regarded as the gold standard diagnostic method for assessing epicardial fat thickness. However, our study did not employ MRI, which stands as a limitation. Nonetheless, it is worth noting that the widespread use of MRI for evaluating epicardial fat on a large scale is not practical. In this context, echocardiography presents itself as a practical, objective, non-invasive, and cost-effective alternative to MRI. Another limitation is the gender imbalance within the AS group, where the prevalence of AS is approximately twice as high in males compared to females (1). This disparity may potentially impact the results when comparing male and female participants within the AS group. Additionally, there is a marginal difference in gender distribution between the study and control groups. While this difference is not statistically significant, it could still impact the study results. We recommend that future studies use gender-matched control groups to minimize potential bias and further validate these findings.

Key strengths of our study include having a control group, echocardiographic evaluations in AS patients conducted by field experts, and the use of diverse analyses enabling a comparative examination. All transthoracic echocardiography was performed by the same cardiologist, and the cardiac examinations were reviewed by two cardiologists, ensuring more precise and consistent results.

Conclusion

As a result, EATT values were higher in AS patients compared to those of the controls in this study. The factors related to EATT were BMI, ESR, BASFI, BASMI, and the grade of sacroiliitis. No significant correlations were identified between EATT and functional capacity, as measured by either the 6-MWT or IPAQ. Since BASFI and BASMI are better markers of chronic inflammation, patients with functional and mobility limitations may benefit from early cardiologic follow-up. It is recommended to conduct further studies with larger sample sizes to confirm our findings.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Local Ethics Committee of Bakırköy Dr. Sadi Konuk Education and Research Hospital and subsequently approved by the Turkish Ministry of Health (decision no: 2016/03/10, date: 11.04.2016).
Informed Consent: Informed consent, both oral and written, was obtained from each patient before their participation in the study.

Footnotes

Authorship Contributions

Concept: A.S., N.K., B.U., A.Y., Design: A.S., N.K., D.B., N.P., Data Collection or Processing: A.S., B.U., N.P., Analysis or Interpretation: N.K., D.B., A.Y., Literature Search: N.K., D.B., B.U., A.Y., N.P., Writing: A.S., N.K., A.Y.
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