Exploring the Link Between Ankylosing Spondylitis and Inflammatory Bowel Disease: A Retrospective Cohort Study

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ABSTRACT **Background:** Ankylosing spondylitis (AS) and inflammatory bowel disease (IBD) are chronic conditions with overlapping pathogenic mechanisms. The genetic predisposition and inflammatory pathways common to both diseases suggest a syndemic relationship. While some evidence points to a connection between the two conditions, other reports do not support this link.

Objectives: To investigate the association between AS and the subsequent incidence of IBD. To identify potential risk factors and effect modifiers that contribute to this relationship.

Methods: Utilizing the Chronic Disease Registry of Clalit Health Services, we conducted a retrospective cohort study of individuals diagnosed with AS between January 2002 and December 2018. We compared these patients with age- and sex-matched controls, excluding those with a prior diagnosis of IBD. Statistical analyses included chi-square and *t*-tests for demographic comparisons, and Cox proportional hazards models for evaluating the risk of IBD development, with adjustments for various co-morbidities and demographic factors.

Results: The study included 5825 AS patients and 28,356 controls. AS patients demonstrated a significantly higher incidence of IBD with hazard ratios of 6.09 for Crohn's disease and 2.31 for ulcerative colitis, after multivariate adjustment. The overall incidence of IBD in the AS cohort was significantly higher compared to controls.

Conclusions: AS patients exhibit a markedly increased risk of developing IBD. These findings advocate for heightened clinical vigilance for IBD symptoms in AS patients and suggest the need for a multidisciplinary approach to patient care. Further research into the shared pathogenic pathways is needed to develop personalized treatment strategies and improve patient management.

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KEY WORDS: ankylosing spondylitis (AS), Crohn's disease, inflammatory bowel disease (IBD), ulcerative colitis

Inflammatory bowel disease (IBD) and ankylosing spondylitis (AS) are chronic conditions that significantly impact patient health and quality of life. IBD primarily affects the gastrointestinal tract and is characterized by Crohn's disease and ulcerative colitis, with a propensity to manifest extraintestinal symptoms, notably spondylarthritis (SpA) [1]. AS is a severe form of SpA, chiefly influencing the axial skeleton, with a predilection for onset before age 40 years and a male demographic dominance. The diagnosis hinges on clinical evaluation of inflammatory back pain and radiographic evidence of sacroiliitis, supplemented by the presence of extra-articular manifestations such as psoriasis, uveitis, and IBD [2].

The intersection of these diseases presents a complex clinical picture, as evidence suggests a shared pathogenic landscape that intertwines their etiologies. The genetic and pathophysiological overlap, notably the human leukocyte antigen (HLA)-B27 gene and the interleukin-23 (IL-23) pathway, underscores a potentially intrinsic connection that predisposes AS patients to the development of IBD [3]. While the prevalence of concurrent AS and IBD is estimated to be between 5–10%, radiologic signs of sacroiliitis appear in up to half of IBD patients. Macroscopic and microscopic bowel inflammation is notable in AS patients, with reports indicating an occurrence in 14–37% and 50–58% of individuals, respectively [4,5]. While some evidence points to a connection between the two conditions, there are also reports that do not support this link.

Understanding the epidemiological link between AS and IBD is crucial for developing effective screening tools, preventive strategies, and personalized treatment approaches. The aim of this study was to elucidate the epidemiological association between ankylosing spondylitis and the

increased incidence of inflammatory bowel disease, with a focus on the risk factors contributing to this association.

PATIENTS AND METHODS

ETHICS CONSIDERATIONS

The investigation into the relationship between AS and subsequent development of IBD was conducted following a protocol approved by the ethics committee of Clalit Health Services. The retrospective nature of the study with adherence to participants' anonymity obviated the need for individual informed consent.

DATA SOURCE: CHRONIC DISEASE REGISTRY OF CLALIT HEALTH SERVICES

This study utilized the extensive central database of Clalit Health Services, the largest integrated health service provider in Israel. This database provides a unique opportunity for comprehensive epidemiological studies due to its coverage of over 4.5 million individuals, approximately 48% of the national population. The data repository encompasses medical and administrative records from an array of health facilities, including hospitals, primary care clinics, specialty clinics, and pharmacies. The integrity of the data is rigorously maintained through multiple verification processes, including logical checks and cross-referencing of diagnoses across various data sources, ensuring high validity as corroborated by prior research [6,7].

STUDY POPULATION

We identified patients diagnosed with ankylosing spondylitis, codified by the ICD-9 Code: 720.0, as recorded by specialist physicians in clinical medical records from 1 January 2002 to 31 December 2018. Cases of IBD were similarly identified using the ICD-9 Code: 555 (Crohn's disease) and 556 (ulcerative colitis). Controls were selected from the same registry, matched by age and sex in a five-to-one ratio to AS patients. Exclusion criteria included a prior diagnosis of IBD. The index date was set to the diagnosis date of AS. Follow-up for each cohort extended to 23 June 2019.

VARIABLES AND DATA COLLECTION

The variables for this study were chosen to ensure a robust analysis. Collected data comprised demographic details (age, sex), socioeconomic status (SES), ethnicity, smoking habits, treatment for ankylosing spondylitis, and a range of co-morbid conditions. SES was calculated using the poverty index from the 2008 national census, which integrates multiple socioeconomic indicators such as household income, education level, housing density, workforce participation, per capita income, and vehicle ownership. This comprehensive index allowed for categorization into low, medium, or high SES groups. Smoking status was simplified to a binary variable reflecting current smoker or non-smoker status. The endpoint of the study was determined by the occurrence of the first event among the following: diagnosis of IBD, death, or the end of the follow-up period.

STATISTICAL ANALYSIS

Differences in baseline characteristics between different groups of independent variables were compared using a *t*-test for continuous variables and a chi-square test for categorical variables. *P*-value < 0.05 was considered statistically significant. We evaluated the interactions between AS and the development of IBD using an analysis of variance (ANOVA) framework. Cox proportional hazards models provided estimates of the hazard ratio (HR) for the incidence of IBD in AS patients versus controls. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using mean values with standard deviations. Adjustment was conducted for age, sex, ethnicity, socioeconomic status, smoking status, and body mass index (BMI). Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 26 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Our study involved 5825 AS patients and 28,356 controls. The mean age of AS patients and controls was 50.0 ± 16 years and 49.8 ± 16 years, respectively, with a median age close to 49 years for both groups. The distribution of sex was similar in both groups, with males constituting 63.5% of AS patients and 63.4% of controls. The proportion of participants with Arab ethnicity was also comparable between AS patients (17.2%) and controls (17.3%).

Smoking history showed a significant difference: 34.9% of AS patients had a smoking history compared to 33.1% of controls ($P < 0.01$). Recruitment periods were evenly distributed across three intervals (2002–2007, 2008–2013, 2014–2018) without significant differences between the groups. SES, categorized as low, medium, and high, was similar in both cohorts.

A notable difference was observed in BMI distribution. While 33.9% of AS patients had a BMI of 18.5–24.9 kg/m², 37.4% of controls had a similar BMI. Conversely, 29.6% of AS patients had a BMI of ≥ 30 kg/m² compared to 23.9% of controls, indicating a higher prevalence of obesity in the AS group ($P < 0.001$).

In terms of AS treatment, 22.8% of patients were taking tumor necrosis factor inhibitors (TNFi), 27.1% any disease-modifying anti-rheumatic drugs (DMARDs), 14.7% DMARDs only, and 61.1% non-steroidal anti-inflammatory drugs (NSAIDs) only [Table 1].

INCIDENCE AND RISK OF IBD IN AS PATIENTS COMPARED TO CONTROLS

The incidence and risk analysis for Crohn's disease, ulcerative colitis, and IBD in AS patients compared to controls revealed significant differences [Table 2]. For Crohn's disease, AS patients had an incidence rate of 17.77 per 10,000 person-years, significantly higher than the 1.58 rate in controls. The unadjusted hazard ratio (HR) was 7.43, and the multivariate-adjusted HR was 6.09, both indicating a substantially increased risk in AS patients.

Similarly, for ulcerative colitis, the incidence rate was higher in AS patients (5.84 per 10,000 person-years) compared to controls (1.58). The unadjusted and multivariate-adjusted HRs were 3.70 and 2.31, respectively, suggesting an increased risk in the AS cohort. When considering IBD, the incidence rate in AS patients was 23.14 per 10,000 person-years versus 3.12 in controls. The unadjusted HR was 11.50 and the multivariate-adjusted HR was 9.18, indicating a significantly higher risk for IBD in AS patients.

Table 1. Baseline characteristics of the study population

Characteristics	AS patients (n=5825)	Controls (n=28,356)	*P*-value
Age, mean ± SD; median	50.0 ± 16; 49.3	49.8 ± 16; 49.1	NS
Men, n (%)	3701 (63.5)	17,975 (63.4.)	NS
Arab ethnicity, n (%)	999 (17.2)	4914, 17.3)	NS
Smoking history, n (%)	2032 (34.9)	9379 (33.1)	<0.01
Recruitment periods, n (%)			NS
2002–2007	1754 (30.1)	8576 (30.2)	
2008–2013	2103 (36.1)	10,212 (36.0)	
2014–2018	1968 (33.8)	9568 (33.7)	
Socioeconomic status*, n (%)			NS
Low	787 (14.4)	4082 (15.4)	
Medium	3837 (70.3)	18,570 (69.9)	
High	834 (17.6)	3907 (14.7)	
Body mass index n (%)**			<0.001
< 18.5 kg/m²	97 (2.3)	469 (2.5)	
18.5–24.9 kg/m²	1413 (33.9)	7029 (37.4)	
25– 29.9 kg/m²	1428 (34.2)	6788 (36.1)	
≥ 30 kg/m²	1235 (29.6)	4499 (23.9)	
AS treatment, n (%)			
TNFi	1330 (22.8)	–	
DMARDs any	1580 (27.1)	–	
DMARDs only	857 (14.7)	–	
NSAIDs only	3560 (61.1)	–	

AS = ankylosing spondylitis, DMARDs = disease modifying anti-rheumatic drugs, IBD = inflammatory bowel disease, NSAIDs = non-steroidal anti-inflammatory drugs, SD = standard deviation, TNFi = tumor necrosis factor inhibitors
*Available for 93.7% of data
**Available for 67.1 % of data

INCIDENCE AND RISK OF IBD IN DIFFERENT AS SUBGROUPS

Further analysis showed variation in IBD incidence and risk across different AS subgroups [Table 3]. In patients aged ≤ 49 years, the HR for IBD was 10.01, whereas it was 5.27 in those > 49 years. Both age groups exhibited significantly increased risks compared to their respective controls. With regard to sex, men with AS had an HR of 7.77, while women had an HR of 6.83 for developing IBD, which was significantly higher than their matched controls. Regarding AS treatment subgroups, patients taking TNFi had an HR of 8.97, those on DMARDs only had an HR of 10.93, and those on NSAIDs only had an HR of 5.50, all indicating elevated risks compared to controls. In Figure 1, we presented a forest plot of IBD risk in AS subgroups compared to matched controls.

DISCUSSION

In our retrospective cohort study, leveraging the extensive Chronic Disease Registry of Clalit Health Services, has revealed a pronounced association between AS and the incidence of IBD. The multivariate adjusted hazard ratio of 6.09 for Crohn's disease and 2.31 for ulcerative colitis highlights the increased risk that AS patients show for developing IBD. The findings indicated that individuals with AS are significantly more likely to develop IBD compared to age- and sex-matched controls without AS.

The link between AS and IBD has been a subject of interest since the 1960s. Early observations by Moll and colleagues [8] indicated a striking association between AS and several other disorders, including IBD. This early work laid the foundation for understanding the complex interplay between these conditions. Subsequently, Meuwissen et al. [9] conducted a study to determine the prevalence of IBD among patients with AS. Among the 79 AS patients screened, 3.8% were diagnosed with IBD, highlighting a potential connection between these conditions. As research in this area progressed, more recent studies have continued to explore this association. Stolwijk's research [10], for example, demonstrated that patients with AS are at a significantly increased risk of developing IBD compared to controls (HR 3.3; 95% confidence interval [95%CI] 2.3–4.8). Bremander and colleagues [11] similarly noted an even

Table 2. Incidence and risk for Crohn's disease, ulcerative colitis and inflammatory bowel disease in ankylosing spondylitis patients compared to controls

Outcomes	Variables	AS (n=5825)	Controls (n=28,355)
Crohn's disease	Events, n (%)	76 (1.3)	35 (0.1)
	Follow-up time, median (IQR)	7.29 (3.4–11.4)	7.52 (3.5–11.7)
	Cumulative patient-years	42,780	221,345
	Incidence rate per 10,000 person-years, (95%CI)	17.77 (14.0–22.24)	1.58 (1.10–2.20)
	Unadjusted HR (95%CI)	7.43 (5.36–10.30)	reference
	Multivariate HR (95%CI)	6.09 (3.91–9.51)	reference
Ulcerative colitis	Events, n (%)	25 (0.4)	35 (0.1)
	Follow-up time, median (IQR)	7.29 (3.4–11.4)	7.52 (3.5–11.7)
	Cumulative patient-years	42,780	221,345
	Incidence rate per 10,000 person-years, (95%CI)	5.84 (3.78–8.63)	1.58 (1.10–2.20)
	Unadjusted HR (95%CI)	3.70 (2.16–6.32)	reference
	Multivariate HR (95%CI)	2.31 (0.99–5.41)	reference
Inflammatory bowel disease	Events, n (%)	99 (1.7)	69 (0.2)
	Follow-up time, median (IQR)	7.29 (3.4–11.4)	7.52 (3.5–11.7)
	Cumulative patient-years	42,780	221,345
	Incidence rate per 10,000 person-years, (95%CI)	23.14 (18.81–28.05)	3.12 (2.45–3.95)
	Unadjusted HR (95%CI)	11.50 (7.48–17.69)	reference
	Multivariate HR (95%CI)	9.18 (5.30–14.38)	reference

Adjusted for age, sex, ethnicity, socioeconomic status, smoking status, and body mass index
95%CI = 95% confidence interval, AS = ankylosing spondylitis, HR = hazard ratio, IQR = interquartile range

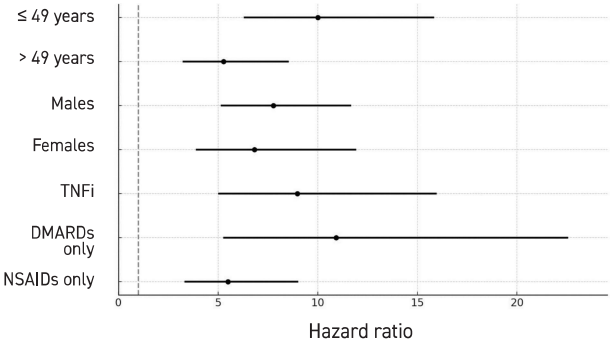
Table 3. Incidence and risk for inflammatory bowel disease in different ankylosing spondylitis subgroups compared to their matched controls

Subgroup	AS, n (%)	Controls, n (%)	HR (95%CI)	*P*-value
Age				
≤ 49 years	54 (1.9)	28 (0.2)	10.01 (6.34–15.80)	< 0.001
> 49 years	34 (1.2)	33 (0.2)	5.27 (3.26–8.50)	< 0.001
Sex				
Male	59 (1.6)	39 (0.2)	7.77 (5.18–11.64)	< 0.001
Female	29 (1.4)	22 (0.2)	6.83 (3.93–11.89)	< 0.001
AS treatment				
TNFi	33 (2.5)	18 (0.3)	8.97 (5.05–15.93)	< 0.001
DMARDs only	22 (2.6)	11 (0.3)	10.93 (5.30–22.53)	< 0.001
NSAIDs only	33 (0.9)	31 (0.2)	5.50 (3.36–8.97)	< 0.001

95%CI = confidence interval, AS = ankylosing spondylitis, DMARDs = disease modifying anti-rheumatic drugs, IBD = inflammatory bowel disease, NSAIDs = non-steroidal anti-inflammatory drugs, HR = hazard ratio, TNFi = tumor necrosis factor inhibitors

Figure 1. Forest plot of inflammatory bowel disease risk in ankylosing spondylitis subgroups compared to matched controls

DMARDs = disease modifying anti-rheumatic drugs, NSAIDs = non-steroidal anti-inflammatory drugs, TNFi = tumor necrosis factor inhibitors



higher rate of IBD among AS patients with standardized morbidity rate ratios of 9.28 (95%CI 7.07–11.97).

However, the assumption that patients with AS have a higher incidence of developing IBD is not universally supported. A study by Lai et al. [12] found no significant increase in the incidence of IBD among AS patients in Taiwan, challenging the notion of a straightforward causal relationship. Lai's study indicated that while AS and IBD might co-occur due to similar pathogenic pathways, one did not necessarily facilitate the development of the other.

Considering these diverse findings in a large cohort, we determined that there is an elevated incidence of IBD in AS patients, which corroborates most of the research [13].

In addition, we explored the precise characteristics of patients with AS who were more likely to develop IBD. The stratified analysis by treatment subgroup revealed intriguing insights. The fact that AS patients on TNFi therapy have an elevated hazard ratio (HR) of 8.97 for developing IBD, despite TNFi's efficacy in treating both AS and IBD, raises questions about the complex interplay between treatment, disease progression, and the onset of co-morbid conditions. This finding might also be explained by the observation that severe forms of AS are treated with biologic medications, and patients with more severe AS are at a higher risk of developing IBD.

Another intriguing aspect of our sub-analysis was the higher incidence of IBD among patients with AS across all age groups. In a related study, Wang et al. [14] also investigated the risk of developing IBD among AS patients. While their cohort was smaller than ours, encompassing 3804 patients with AS and 7608 non-AS patients, their findings are noteworthy. The Kaplan-Meier curves depicting the cumulative incidence of IBD indicate that AS patients are at a higher risk of developing IBD compared to non-AS patients. However, this increased risk was notably evident only in patients under 40 years of age (HR 2.85, 95%CI 1.51–5.40). Interestingly, they did not observe a similar elevation in risk among the age groups of 40–64 and older than 65 years.

The elevated incidence of IBD in AS patients observed in our study corroborates previous research suggesting a shared pathogenic mechanism between these conditions. The association between these conditions is anchored in the gut-synovial axis hypothesis, which highlights the role of environmental factors and genetic predisposition in initiating inflammation [15]. The role of bacterial antigens and reactive T-cell clones, activated in the gut and homing to the joints, is pivotal yet not fully understood. Moreover, genetic predisposition, including the presence of specific HLA alleles like HLA-B27, HLA-B35, and HLA-B44, plays a significant role in this link [16].

Central to the connection between AS and IBD is the IL-23/IL-17 axis, which plays a crucial role in both conditions. This axis is regulated primarily by IL-23, which stimulates the production of cytokines like IL-17, IL-22, and TNF by Th17 cells and other immune cells. In the guts of Crohn's disease patients or those with SpA, an increased expression of IL-23 has been observed. Simi-

larly, in AS patients, there is an elevated presence of IL-23R expressing Tγδ cells and increased production of IL-17, suggesting a critical role of the IL-23/-17 axis in the pathogenesis of both AS and IBD [17].

Our study's robust methodology and the utilization of a large, representative database strengthen the validity of these findings. The inclusion of a wide array of co-morbidities and socioeconomic variables in the fully adjusted models mitigates potential confounding factors, providing a clearer picture of the relationship between AS and IBD.

Despite the study's strengths, we acknowledge several limitations. The retrospective design inherently limited our ability to establish causality. Although we adjusted for a broad range of co-morbidities and demographic factors, residual confounding by unmeasured variables, such as dietary patterns and physical activity levels, cannot be excluded. The reliance on ICD-9 codes for diagnosis could introduce a misclassification bias. However, the high validity of the Clalit database, as demonstrated in previous studies, mitigated this concern [18,19]. Moreover, the lack of data on medication adherence and the duration of AS before the study period may influence the observed association with IBD. Another limitation is the generalizability of the findings. Our study population, derived from a single health service in Israel, may not reflect the experience of different ethnicities or healthcare systems. Therefore, caution should be exercised when extrapolating these results to other populations.

CONCLUSIONS

We found a significant epidemiological association between AS and the increased incidence of IBD. The findings underscore the necessity for heightened clinical awareness and monitoring for IBD in patients with AS. Further research is needed into the underlying mechanisms of this association, which could lead to improved management and therapeutic strategies for these patients.

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References

1. Savin E, Ben-Shabat N, Levartovsky A, et al. Biologic treatment modification efficacy in concurrent inflammatory bowel disease and ankylosing spondylitis: a retrospective cohort study at a single tertiary center. *J Clin Med* 2023; 12 (22): 7151.
2. Rudwaleit M, Baeten D. Ankylosing spondylitis and bowel disease. *Best Pract Res Clin Rheumatol* 2006; 20 (3): 451-71.
3. Sharif K, Bridgewood C, Dubash S, McGonagle D. Intestinal and enthesis innate immunity in early axial spondyloarthropathy. *Rheumatology (Oxford)* 20201; 59 (Suppl4): iv67-iv78.
4. Xiong Y, Cai M, Xu Y, Dong P, Chen H, He W, Zhang J. Joint together: the etiology and pathogenesis of ankylosing spondylitis. *Front Immunol* 2022; 13: 996103.
5. Van Praet L, Van den Bosch FE, Jacques P, et al. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. *Ann Rheum Dis* 2013; 72 (3): 414-7.
6. Omar M, Ben-Shabat N, Tsur Amet al. The association between ankylosing spondylitis and psychiatric disorders: Insights from a population based cross-sectional database. *J Affect Disord* 2023; 323: 788-92.
7. Patt YS, Ben-Shabat N, Fisher L, Amital H, Watad A, Sharif K. The prevalence of dementia among dermatomyositis and polymyositis patients: a retrospective cohort study. *IMAJ* 2023; 25 (7): 479-84.
8. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore)* 1974; 53 (5): 343-64.
9. Meuwissen SG, Dekker-Saeys BJ, Agenant D, Tytgat GN. Ankylosing spondylitis and inflammatory bowel disease. I. Prevalence of inflammatory bowel disease in patients suffering from ankylosing spondylitis. *Ann Rheum Dis* 1978; 37 (1): 30-2.
10. Stolwijk C, Essers I, van Tubergen A, et al. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. *Ann Rheum Dis* 2015; 74 (7): 1373-8.
11. Bremander A, Petersson IF, Bergman S, Englund M. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. *Arthritis Care Res (Hoboken)* 2011; 63 (4): 550-6.
12. Lai SW, Kuo YH, Liao KF. Incidence of inflammatory bowel disease in patients with ankylosing spondylitis. *Ann Rheum Dis* 2021; 80 (9): e144.
13. Carubbi F, Alunno A, Viscido A, et al. SpA plus IBD or IBD plus SpA: does commutative property apply? *Autoimmun Rev* 2023; 22 (10): 103443.
14. Wang S, Tsou HK, Chiou JY, Wang YH, Zhang Z, Wei JC. Increased risk of inflammatory bowel disease among patients with ankylosing spondylitis: a 13-year population-based cohort study. *Front Immunol* 2020; 11: 578732.
15. Fragoulis GE, Liava C, Daoussis D, Akriviadis E, Garyfallos A, Dimitroulas T. Inflammatory bowel diseases and spondyloarthropathies: from pathogenesis to treatment. *World J Gastroenterol* 2019; 25 (18): 2162-76.
16. Orchard TR, Thiyagaraja S, Welsh KI, Wordsworth BP, Hill Gaston JS, Jewell DP. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. *Gastroenterology* 2000; 118 (2): 274-8.
17. Ciccia F, Bombardieri M, Principato A, et al. Overexpression of interleukin-23, but not interleukin-17, as an immunologic signature of subclinical intestinal inflammation in ankylosing spondylitis. *Arthritis Rheum* 2009; 60 (4): 955-65.
18. Sharif K, Watad A, Tiosano S, et al. The link between COPD and ankylosing spondylitis: a population based study. *Eur J Intern Med* 2018; 53: 62-65.
19. Sharif K, Sci AM, Watad A, et al. Familial Mediterranean fever association with schizophrenia: insights from big data analysis. *Arch Med Sci [Internet]* 2020; [Available from https://www.archivesofmedicalscience.com/Familial-Mediterranean-fever-association-with-schizophrenia-insights-from-big-data,118485,0,2.html].