Send Orders for Reprints to reprints@benthamscience.net

Current Cardiology Reviews, 2021, *17*, e150521193326

META-ANALYSIS

Ankylosing Spondylitis and Risk of Cardiac Arrhythmia and Conduction Disorders: A Systematic Review and Meta-analysis

Negar Morovatdar[1], Gerald F. Watts[2], Yones Bondarsahebi[3,4], Fatemeh Goldani[3,4], Elham Rahmanipour[3,4], Ramin Rezaee[1] and Amirhossein Sahebkar[5,6,7,8,9,*]

[1]Clinical Research Development Unit, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran; [2]Department of Cardiology, Cardiometabolic Service, School of Medicine, Royal Perth Hospital, The University of Western Australia, Perth, Australia; [3]Students Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [4]Evidence Based Medicine Research Group, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [5]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran; [6]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; [7]School of Medicine, The University of Western Australia, Perth, Australia; [8]Halal Research Center of IRI, FDA, Tehran, Iran; [9]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE HISTORY

Received: October 18, 2020
Revised: January 10, 2021
Accepted: February 17, 2021

DOI:
10.2174/1573403X17666210515164206

Abstract: ***Objective*:** The objective of this study isto assess the association between ankylosing spondylitis (AS) and risk of heart conduction disorders and arrhythmia.

***Methods*:** PubMed, Embase, and Web of Science databases were systematically searched for observational studies that investigated the association between AS and risk of heart conduction disorders and arrhythmia with no language or date restrictions until September 16, 2019. We used random- and fixed-effects models to pool the results of the studies. Publication bias was assessed by Egger's test. Subgroup analysis was carried out based on the study design. A p-value less than 0.05 was considered significant. Comprehensive Meta-Analysis (CMA) software was used to perform meta-analysis.

***Results*:** After removing duplicates, we reviewed 135 articles. Finally, we included seven articles in our meta-analysis, of which four studies reported AV block and any conductive abnormality and three focused on atrial fibrillation and any arrhythmia. Based on our meta-analysis, an increased risk of atrial fibrillation (RR: 1.85, 95%CI: 1.15-2.98) and atrioventricular block (OR: 3.46, 95%-CI: 1.09-10.93) was found in AS subjects compared to the general population. In a subgroup analysis based on study design, we found a greater association between AS and atrioventricular block in cohort studies (RR: 5.14, 95%CI: 1.001-26.50) compared to cross-sectional ones. However, we did not find any association between AS and any arrhythmia (OR=3.36, 95% CI: 0.93-12.15), or conduction disorders (OR: 0.64, 95%CI: 0.38-1.06). No publication bias was found.

***Conclusion*:** Our results support an association between AS and a higher risk of atrial fibrillation and atrioventricular block.

Keywords: Ankylosing spondylitis, rheumatology, cardiovascular disease, arrhythmia, systematic review, meta-analysis.

1. INTRODUCTION

Ankylosing spondylitis (AS) is a rheumatological disorder characterized by inflammatory involvement of the sacroiliac and spinal joints and a marked association with human leukocyte antigen (HLA)-B27 [1]. The incidence of AS is 0.5-14 per 100,000 people per year, worldwide [2]. Interactions between bacteria and HLA-B27 were shown to significantly contribute to disease pathogenesis in models of spondyloarthritides [1]. Based on a previous study, there is a 25% increased risk of cardiovascular disease (CVD) in valvular heart disease, ischemic heart disease, congestive heart failure and other cardiovascular diseases in AS patients [3]. Recent researches have confirmed the effects of systemic inflammation in AS on different parts of the heart such as cardiac valves, conduction system, myocardium and vessels that can result in cardiovascular disturbances [4]. Some, but not all studies, have suggested an increased risk of cardiac conduction abnormalities in AS patients; however, the magnitude of the risk contributed by AS is unclear. This study systematically reviewed reports that presented the risk of cardiac arrhythmia and conduction abnormalities in AS patients compared with the general population. We al-

* Address correspondence to this author at the Department of Medical Biotechnology, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran; E-mail: amir_saheb2000@yahoo.com

so aimed to estimate the size of the mentioned risk by performing a meta-analysis of the studies.

2. METHODS

2.1. Eligibility Criteria

The present work covered observational reports (*i.e.* cohort, case-control and cross-sectional studies) discussing the risk of any type of arrhythmia/conduction disorders in AS patients compared with the healthy people according to the protocol of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [5]. Systematic reviews, case reports/case series and congress abstracts as well as studies that did not meet the inclusion criteria or those that reported duplicate data, were excluded. We used the International Classification of Diseases, the tenth Revision, Clinical Modification (ICD-10) codes 144, 145, 146, 147, 148, and 149 to identify all patients with various arrhythmias such as atrial fibrillation (AF), supraventricular tachycardia, Wolff–Parkinson–White syndrome and conduction disorders such as and AV-blocks and bundle branch blocks [6].

2.2. Search Strategy

PubMed, Web of Science and Embase databases were systematically searched for articles indexed until September 16, 2019, using the following keywords: "Ankylosing Spondylitis", "Bechterew Disease", "Marie Struempell Disease", "Rheumatoid Spondylitis", "Ankylosing Spondyloarthritis", "Sinoatrial Arrhythmia", "Atrial Fibrillations", "Atrial Flutter", "Bradycardia", "Brugada Syndrome", "Premature Beats", "Cardiac Concussions", "Heart Blocks", "Atrioventricular Dissociations", "Tachycardia", "Ventricular Fibrillation", "Ventricular Flutters", "Cardiac Dysrhythmia", "Cardiac Arrhythmia", and "WPW Syndrome" (Supplementary Table **1**).

2.3. Selection Process

Two reviewers (FG and ER) independently checked out the articles in two steps; first, they merely reviewed the titles and abstracts. After the selection of articles, based on the inclusion criteria considered in the title abstraction selection step, the full texts were reviewed to select the relevant studies. Finally, the articles that compared the frequency of any type of conduction disorders and/or arrhythmia in AS patients with healthy controls or reported odd ratio (OR) or relative risk (RR), were selected. Eventually, articles which were not selected by either of the reviewers were assessed once more by a third reviewer (NM).

2.4. Quality Assessment

The quality of the studies was evaluated by the Joanna Briggs Institute Critical Appraisal Checklist for cross-sectional and cohort studies. This checklist consists of 8 items based on which, two reviewers individually evaluated each article and double-checked in case of noncompliance. Articles with a score 5 ≥ were contemplated as "high-quality" ones and were eligible to be included in our systematic review.

2.5. Data Extraction

The data extraction form was filled for selected studies and used to abstract general information about the paper (*i.e.* first author's name, year of publication, sample size, event number and total sample size in each group, place of study, study characteristics, study population, type of conduction disorders and arrhythmia, method of assessment of conduction disorders and AS disease, design features that affected the study quality and the validity of the results and outcome measures).

2.6. Statistical Analysis

To assess possible associations, summary data from individual studies was pooled using a fixed- or random-effect model. All proportional data were summarized as OR or RR along with 95% confidence intervals (CIs). The inconsistency index (I^2) was used to measure heterogeneity, with an $I^2 >$ 50% indicating substantial heterogeneity. Subgroup analysis was done based on study design (cohort *versus* cross-sectional). Using Egger's test, publication bias was assessed. All analyses were performed using Stata version 11 and a p-value <0.05 was considered statistically significant.

3. RESULTS

The inclusion and exclusion of articles are detailed in (Fig. **1**). A total of seven studies compared the frequency of arrhythmia/conduction disorders between AS patients and a control group (Table **1**). Three of these studies were cohort and four had a cross-sectional design.

Random-effects meta-analysis showed an increased risk of any arrhythmia in AS patients compared with controls (OR=3.36, 95% CI: 0.93-12.15) but the difference did not reach a significant level (p=0.08). Subgroup analysis based on the study design (cohort *versus* cross-sectional), indicated a significant increase in cohort studies but not in cross-sectional ones (Fig. **2**). No publication bias was found (p=0.16).

Using random-effect model, the risk of atrial fibrillation increased in AS patients compared with the controls (RR: 1.85, 95%CI:1.15-2.98; Fig. **3**). Egger's test found no publication bias (p=0.2).

Based on fixed-effect model meta-analysis, no association was observed between the risk of conductive disorders and AS (OR: 0.64, 95%CI: 0.38-1.06; Fig. **4**). No publication bias was found by Egger's test (p=0.6).

Based on our assessment using random-effect model meta-analysis, risk of AV block increased in AS patients compared with control group (OR: 3.46, 95%CI: 1.09-10.93). Subgroup analysis done according to study design revealed a greater association in cohort studies compared with cross-sectional studies (Fig. **5**). Egger's test did not indicate any publication bias (p=0.9).

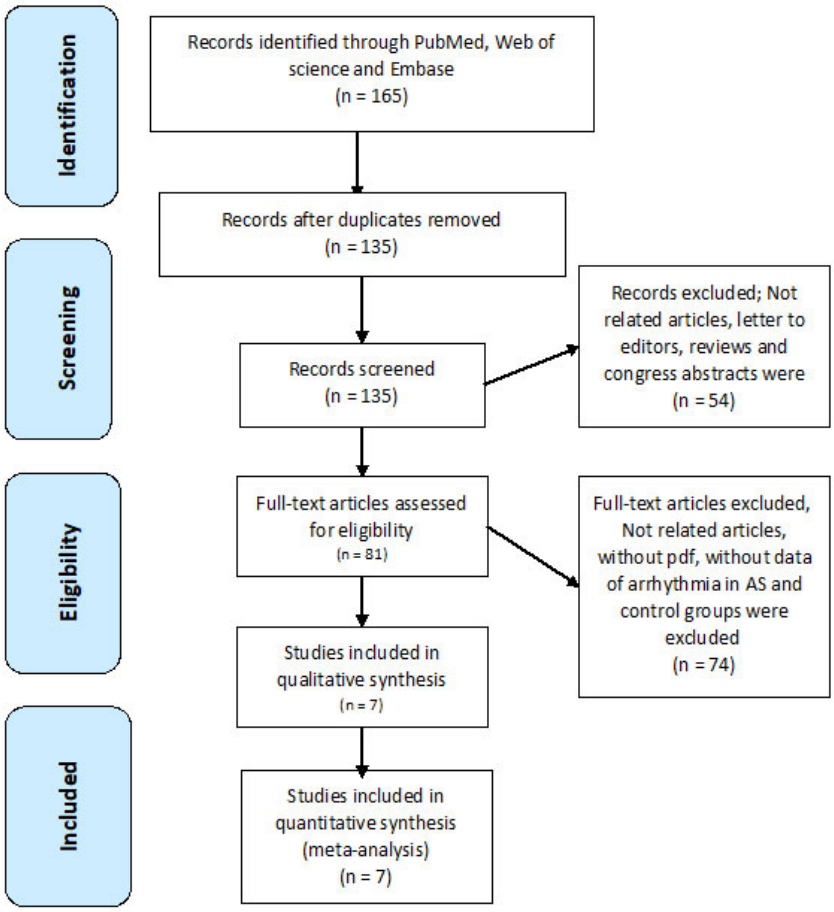

Fig. (1). Flow diagram of study selection process. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Characteristics of the studies included in the analyses.

-	Study Design	Country	Sample Size	How Diagnosis of AS was made	How Arrhythmia / Conduction Disorders were Evaluated
Huei-Huang Ho [17]	Cohort	Taiwan	48009	New York criteria for AS	ECG
Inki Moon [10]	Cohort	Korea	84774	ICD-10-CM	NA
Mohsen Soroush [20]	Cross sectional	Iran	90	New York criteria for AS	physical examination, ECG, echocardiography.
A. Yildirir [21]	Cross sectional	Turkey	119	New York criteria for AS	clinical examination, ECG, 24-hour Holter monitoring.
Florian Brunner [22]	Cross sectional	Switzerland	100	Clinical examination, some cases X-rays	Resting ECG
T. Douglas Kinsella [23]	Cross sectional	Canada	196	Kellgren criteria	Conventional ECGs
Karin Bengtsson [24]	Cohort	Sweden	294136	Clinical examination	Diagnosis from either inpatient or outpatient care.

Abbreviation: ECG: Electrocardiogram.

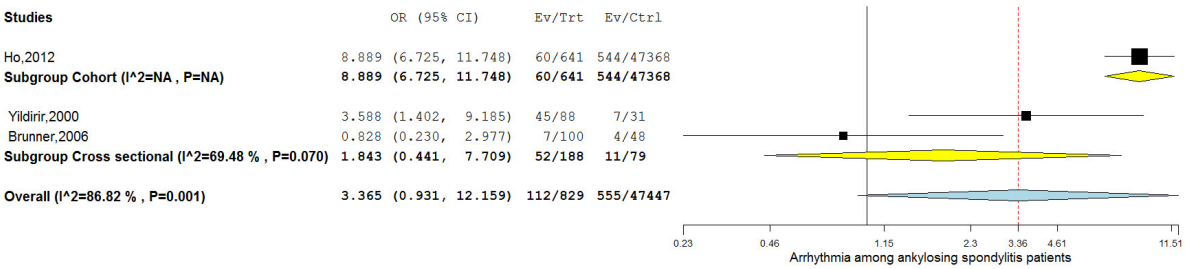

Fig. (2). Forest plot showing the association between ankylosing spondylitis and risk of any arrhythmia. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

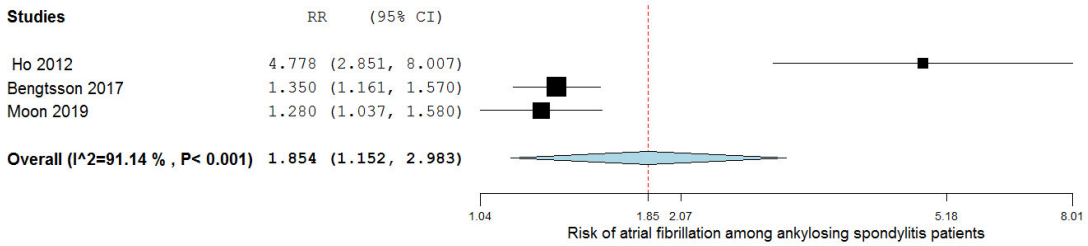

Fig. (3). Forest plot showing the association between ankylosing spondylitis and risk of atrial fibrillation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

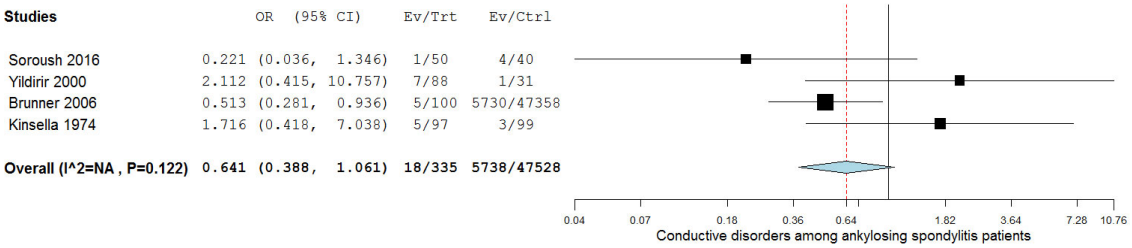

Fig. (4). Forest plot showing the association between ankylosing spondylitis and risk of conductive disorders. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

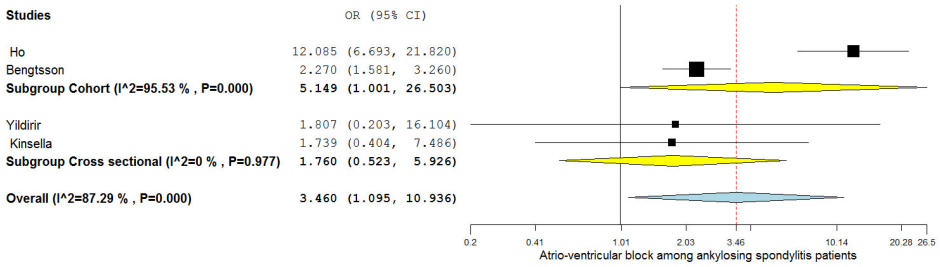

Fig. (5). Forest plot showing the association between ankylosing spondylitis and risk of AV block. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. DISCUSSION

The present systematic review and meta-analysis showed an increased risk of AF and AV block in AS patients. This is the first study that systematically reviewed and investigated possible associations between AS and the development of any type of arrhythmia, AF, AV block or conduction disorders.

We found that in AS patients, there is a 1.8-time higher risk of AF compared with the individuals without AS. Ankylosing spondylitis (AS), as a chronic inflammatory rheumatic disease, is associated with a number of cardiovascular conditions [7]. Inflammation is a major contributor to arrhythmia occurrence [8]. Several inflammatory factors, such as interleukin (IL)-2, IL-6, IL-8, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α), have been reported to be associated with the pathogenesis of AF [9]. In a prospective cohort study conducted in Korea, it was found that AS patients receiving TNF inhibitor (TNFi) had a higher risk of AF development compared with those not receiving TNFi [10]. This finding could be related to a higher severity in these patients for whom non-steroidal anti-inflammatory drugs (NSAIDs) and conventional disease-modifying anti-rheumatic drugs could not control the disease symptoms [11]. These results support the association between inflammation and AF.

Our results showed that AS patients had a higher (up to 3.5 times) risk of AV block occurrence. AS belongs to a cluster of rheumatological diseases with a spectrum of similar clinical features and a varying degree of association with HLA-B27 (human leukocyte antigen (HLA) class I molecule B27) [12]. HLA-B27 was reported to be linked to conduction disturbances and aortic regurgitation, even in the absence of rheumatic diseases [13]. In over 90% of AS patients, a positive HLA-B27 was reported [13]. It was shown that obliterative (occlusive) endarteritis of small vessels supplying the aortic root and the AV node, is a marked histological characteristic described near troubled joints [14]. The inflammatory process involves the development of fibrosis, which might contribute to cardiac involvement [15].

Our analysis did not suggest an association between AS and any conduction disorders or arrhythmia. Other studies reported a higher incidence of aortic valve disease and AV conduction disturbance in AS patients with severe spondylitis, prolonged duration, prominent systemic manifestations and peripheral arthritis [16]. A study found higher rates of acute uveitis, peripheral arthritis, and bamboo spine in AS patients with paroxysmal supraventricular tachycardia (PSVT) or Wolff-Parkinson-White (WPW) syndrome. Similar to uveitis, these findings support the notion that PSVT or WPW syndrome development is associated with higher disease activity and severity in AS [17].

In AS, the destructive pathological process associated with excessive fibrosis affects not only the heart and large vessels but also the epicardium, conduction system, and myocardium. Conduction disturbances usually precede other cardiac symptoms, especially aortal insufficiency [18]. Involvement of the myocardium is a recognized feature of the pathological process; however, reports focusing on arrhythmias in AS are scarce [19]. The present study has the following limitations. Differences in the type of arrhythmia and conduction disorders reported by the retrieved studies might have led to failure in finding an association between AS and conduction disorders and any type of arrhythmia in our meta-analysis. Also, as few studies had focused on this subject, limited data were available for meta-analysis.

CONCLUSION

In conclusion, the present meta-analysis suggests a significant association between AS and AF and AV block. Our findings highlight that patients with AS should be routinely evaluated for conduction disorders of the heart, such as AF and AV block. As specific characteristics of AS that predispose to cardiac complications remain unclear, it is highly recommended to address the gap in future studies.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines have been followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Clinical Research Development Unit, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, assistance in this work.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published work.

REFERENCES

[1] Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007; 369(9570): 1379-90. http://dx.doi.org/10.1016/S0140-6736(07)60635-7 PMID: 17448825

[2] Bakland G, Nossent HC, Gran JT. Incidence and prevalence of ankylosing spondylitis in Northern Norway. Arthritis Rheum 2005; 53(6): 850-5. http://dx.doi.org/10.1002/art.21577 PMID: 16342091

[3] Szabo SM, Levy AR, Rao SR, *et al.* Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: a population-based study. Arthritis Rheum 2011;

63(11): 3294-304.
http://dx.doi.org/10.1002/art.30581 PMID: 21834064

[4] Buleu F, Sirbu E, Caraba A, Dragan S. Heart involvement in inflammatory rheumatic diseases: A systematic literature review. Medicina 2019; 55(6): 249.
http://dx.doi.org/10.3390/medicina55060249 PMID: 31174287

[5] Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4(1): 1.
http://dx.doi.org/10.1186/2046-4053-4-1 PMID: 25554246

[6] World Health Organization. International statistical classification of diseases and related health problems: 10th revision (ICD-10) Available from: http://www. who. int/classifications/apps/icd/icd1992.

[7] O'Neill TW, Bresnihan B. The heart in ankylosing spondylitis. Ann Rheum Dis 1992; 51(6): 705-6.
http://dx.doi.org/10.1136/ard.51.6.705 PMID: 1616349

[8] Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol 2010; 21(9): 1064-70.
http://dx.doi.org/10.1111/j.1540-8167.2010.01774.x PMID: 20455973

[9] Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol 2012; 60(22): 2263-70.
http://dx.doi.org/10.1016/j.jacc.2012.04.063 PMID: 23194937

[10] Moon I, Choi EK, Jung JH, *et al.* Ankylosing spondylitis: A novel risk factor for atrial fibrillation - A nationwide population-based study. Int J Cardiol 2019; 275: 77-82.
http://dx.doi.org/10.1016/j.ijcard.2018.10.024 PMID: 30360993

[11] Braun J, van den Berg R, Baraliakos X, *et al.* 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011; 70(6): 896-904.
http://dx.doi.org/10.1136/ard.2011.151027 PMID: 21540199

[12] Sieper J, Rudwaleit M, Khan MA, Braun J. Concepts and epidemiology of spondyloarthritis. Best Pract Res Clin Rheumatol 2006; 20(3): 401-17.
http://dx.doi.org/10.1016/j.berh.2006.02.001 PMID: 16777573

[13] Peeters AJ, ten Wolde S, Sedney MI, de Vries RR, Dijkmans BA. Heart conduction disturbance: an HLA-B27 associated disease. Ann Rheum Dis 1991; 50(6): 348-50.
http://dx.doi.org/10.1136/ard.50.6.348 PMID: 2059077

[14] Engfeldt B, Romanus R, Ydén S. Histological studies of pelvospondylitis ossificans (ankylosing spondylitis) correlated with clinical and radiological findings. Ann Rheum Dis 1954; 13(3): 219-28.
http://dx.doi.org/10.1136/ard.13.3.219 PMID: 13198056

[15] Brewerton DA, Gibson DG, Goddard DH, *et al.* The myocardium in ankylosing spondylitis. A clinical, echocardiographic, and histopathological study. Lancet 1987; 1(8540): 995-8.
http://dx.doi.org/10.1016/S0140-6736(87)92268-9 PMID: 2883391

[16] Stamato T, Laxer RM, de Freitas C, *et al.* Prevalence of cardiac manifestations of juvenile ankylosing spondylitis. Am J Cardiol 1995; 75(10): 744-6.
http://dx.doi.org/10.1016/S0002-9149(99)80672-9 PMID: 7900679

[17] Ho HH, Yeh SJ, Tsai WP, Wang CM, Chen JY. Paroxysmal supraventricular tachycardia and Wolff-Parkinson-White syndrome in ankylosing spondylitis: a large cohort observation study and literature review. Seminars in arthritis and rheumatism 2012; 42(3): 246-53.
http://dx.doi.org/10.1016/j.semarthrit.2012.04.002

[18] Liu SM, Alexander CS. Complete heart block and aortic insufficiency in rheumatoid spondylitis. Am J Cardiol 1969; 23(6): 888-92.
http://dx.doi.org/10.1016/0002-9149(69)90387-7 PMID: 5785168

[19] Thomsen NH, Hørslev-Petersen K, Beyer JM. Ambulatory 24-hour continuous electrocardiographic monitoring in 54 patients with ankylosing spondylitis. Eur Heart J 1986; 7(3): 240-6.
http://dx.doi.org/10.1093/oxfordjournals.eurheartj.a062058 PMID: 2423334

[20] Soroush M, Mominzadeh M, Ghelich Y, Soroosh S, Pasha MA. Investigation of cardiac complications and their incidence in patients with ankylosing spondylitis. medical archives 2016; 70(1): 35.

[21] Yildirir A, Aksoyek S, Calguneri M, *et al.* QT dispersion as a predictor of arrhythmic events in patients with ankylosing spondylitis. Rheumatology (Oxford) 2000; 39(8): 875-9.
http://dx.doi.org/10.1093/rheumatology/39.8.875 PMID: 10952742

[22] Brunner F, Kunz A, Weber U, Kissling R. Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients with diagnosed ankylosing spondylitis for over 15 years than in the normal population? Clin Rheumatol 2006; 25(1): 24-9.
http://dx.doi.org/10.1007/s10067-005-1117-6 PMID: 16247583

[23] Kinsella TD, Johnson LG, Ian R. Cardiovascular manifestations of ankylosing spondylitis. Can Med Assoc J 1974; 111(12): 1309-11.
PMID: 4442013

[24] Bengtsson K, Forsblad-d'Elia H, Lie E, *et al.* Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. Ann Rheum Dis 2018; 77(4): 541-8.
http://dx.doi.org/10.1136/annrheumdis-2017-212189 PMID: 29259045