Prevalence of Cardiovascular Disease in Patients with Ankylosing Spondylitis: An Analysis from a Nationwide Thailand Healthcare Database

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Abstract

Background: Chronic inflammation of Ankylosing spondylitis (AS) may be associated with cardiovascular disease (CVD). However, the association remains controversial.
Objectives: To determine whether patients with AS are at risk for CVD and the impact of atherosclerosis risk disease in AS.
Methods: We conducted a descriptive study based on a nationwide Thailand healthcare database, using ICD-10 of AS (M45). CVD was defined as either myocardial infarction (MI) (I20-I25), stroke (G45, I63, I69), peripheral arterial disease (I74), heart failure (HF) (I50), cardiomyopathy (I42), aortic valve disease (I35) or arrhythmia (I44). Atherosclerosis risk diseases were defined as either diabetes mellitus (DM) (E10, E11, E13), Hypertension (HT) (I10, I15), or dyslipidemia (DLD) (E78). A total of 766 hospitalized AS patients were included in the analysis. The odds ratio (OR) was calculated to define the risk of CVD and atherosclerosis risk disease.
Results: The mean age was 51 years, 74% were male. The respective highest prevalence of CVD and atherosclerosis risk disease was HF (2.9%) and HT (23%). Patients with HT, DM, or DLD were increased risk of stroke with OR 12.10 (95%CI 4.01-36.55), HT or DLD were increased risk of MI with OR 8.06 (95%CI 2.68-24.34), HT and DLD increased risk of aortic valve disease OR 6.37 (95%CI 1.63-24.88), HT increased risk of cardiac arrhythmias with OR 3.80 (95%CI 1.52-9.50), and DLD increased risk of HF with OR 3.68 (95%CI 1.31-10.36).
Conclusions: The prevalence of CVD is infrequently found in AS patients. The presence of atherosclerosis risk disease consistently increases the risk of CVD.

Keywords: Ankylosing spondylitis, Cardiovascular disease, Atherosclerosis risk disease

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Introduction and Objectives

Ankylosing Spondyloarthritis (AS) is an inflammatory rheumatic disease. The axial skeleton had been affected and presented with characteristic particularly inflammatory back pain. (1) Chronic inflammation may result in the dysfunction of many organs, especially the cardiovascular system. Previous studies have shown that rheumatoid arthritis, a chronic inflammation disease, is associated with an increased incidence of cardiovascular disease and several studies have reported that AS patients have a high risk for myocardial infarction, stroke(2,3) peripheral arterial disease, heart failure, cardiomyopathy, aortic valve disease, and arrhythmias(4,5). The main treatment for AS is non-steroidal anti-inflammatory drugs (NSAIDs), long-term use of NSAIDs may cause and worsen cardiovascular disease. Moreover, AS was associated with an increase in venous thromboembolism when compared to the general population(6).

At present, there is no clear evidence that ankylosing spondyloarthritis is related to cardiovascular disease. This study aimed to determine the prevalence of cardiovascular disease and the impact of atherosclerosis risk disease in patients with ankylosing spondyloarthritis.

Methods

The study was approved by the research ethics board at Khon Khen University Center.

Study setting and data collections

This study was a retrospective cross-sectional descriptive study using the In-patient database. from a National Health Security Office which is a nationwide Thailand healthcare database. A total of 766 AS patients aged 18 years old or older, were hospitalized between January 1, 2014, and December 31, 2018. All patient demographic characteristics were collected such as age, gender, comorbidities, cardiovascular diseases, length of hospital stay (LOS), and discharge status.

Definition

Ankylosing Spondylitis was defined by the International Classification of Disease, 10th Revision (ICD-10) code M45.

Cardiovascular diseases were classified into 7 diseases: 1) myocardial infarction (MI) was defined by ICD10 code I20 to I25, 2) stroke was defined by ICD10 codes G45, I63, and I69, 3) peripheral arterial disease (PAD) was defined by ICD10 code I74, 4) heart failure (HF) was defined by ICD10 code I50, 5) cardiomyopathy was defined by ICD10 code I42, 6) aortic valve disease (AV disease) was defined by ICD10 code I35, and 7) arrhythmia was defined by ICD10 codes I44, I47, and I48.

Atherosclerosis risk diseases were classified into 3 diseases: 1) diabetes mellitus(DM) was defined by ICD10 codes E10, E11, and E13, 2) Hypertension(HT) was defined by ICD10 codes I10, and I15, and 3) Dyslipidemia(DLD) was defined by ICD10 code E78.

Outcomes

Our primary outcome was the prevalence of cardiovascular diseases. A Secondary outcome was the prevalence of atherosclerosis risk diseases and the comparison of cardiovascular events in AS patients with or without atherosclerosis risk diseases.

Statistical analysis

The descriptive statistics were used suitably. Qualitative variables were described by frequency and percentage. Quantitative variables were described by means and standard deviations. The correlation between cardiovascular disease and atherosclerosis risk disease was analyzed by Pearson correlation. A p-value of less than 0.05 was considered statistical significance. SPSS version 26 was used for all analyses in this study.

Results

The total number of AS patients who were admitted to the hospital between January 1, 2014, and December 31, 2018 was 766. The participant characteristics are summarized in Table 1. The mean age of patients was 51.39 years (SD, 17.32), and 74.02% were male. Most of the participants did not have atherosclerosis risk disease.

Primary outcome

The prevalence of cardiovascular diseases is shown in **Table 1.** and **Figure 1.** Stroke and heart failure are the two most prevalent cardiovascular diseases in AS patients.

Secondary outcome

The prevalence of atherosclerosis risk disease in AS patients is shown in **Table 1.** and The comparison of cardiovascular diseases in AS patients with or without atherosclerosis risk diseases is shown in **Figure 2.** Hypertension is an important comorbidity in all cardiovascular diseases.

Table 1: Demographic and Characteristics of Patients (N=766)

Characteristics	N (%)
Male, n (%)	567 (74.02)
Age (years), mean ± SD	51.39 ± 17.32
Atherosclerosis risk disease	
• Diabetes mellitus	80 (10.44)
• Hypertension	179 (23.37)
• Dyslipidemia	60 (7.83)
• No risk	553 (72.76)
Cardiovascular disease	
• Myocardial infarction	16 (2.09)
• Stroke	20 (2.61)
• Heart failure	22 (2.87)
• Cardiomyopathy	8 (1.04)
• Aortic valve disease	11 (1.44)
• Arrhythmias	19 (2.48)
• Peripheral arterial disease	0 (0)
Discharge status	
• Complete recovery	3 (0.39)
• Improve	671 (87.60)
• Not improve	36 (4.70)
• Dead	38 (4.96)
• Others	18 (2.34)
LOS (days), mean ± SD	9.29 ± 4.92

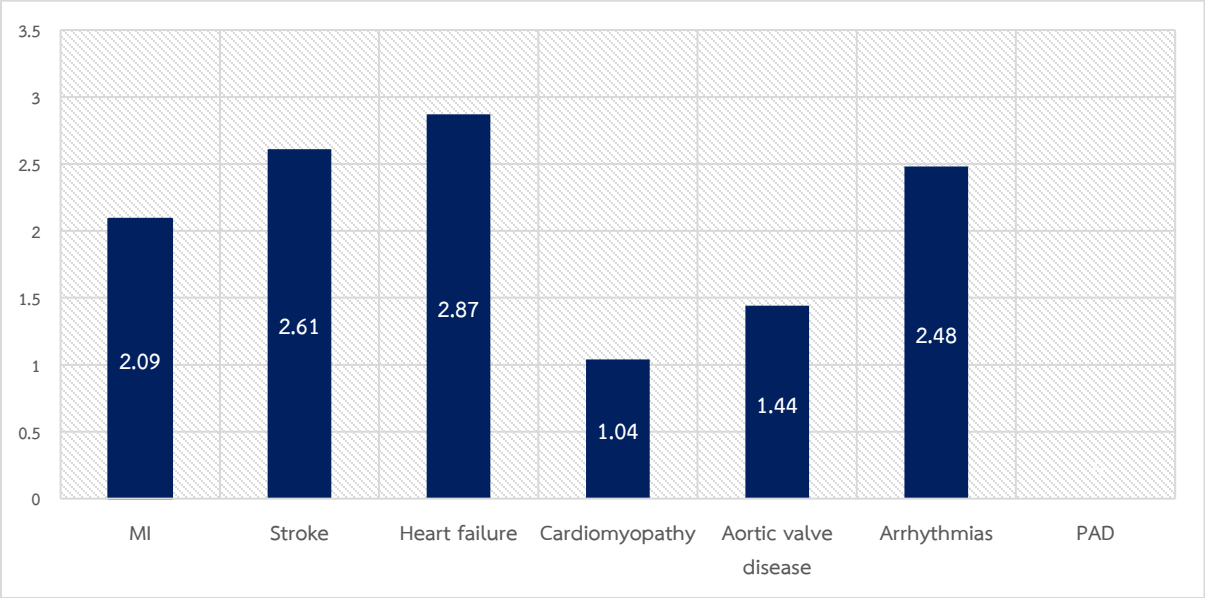

Figure 1: Prevalence of Cardiovascular Disease in AS patients (%)

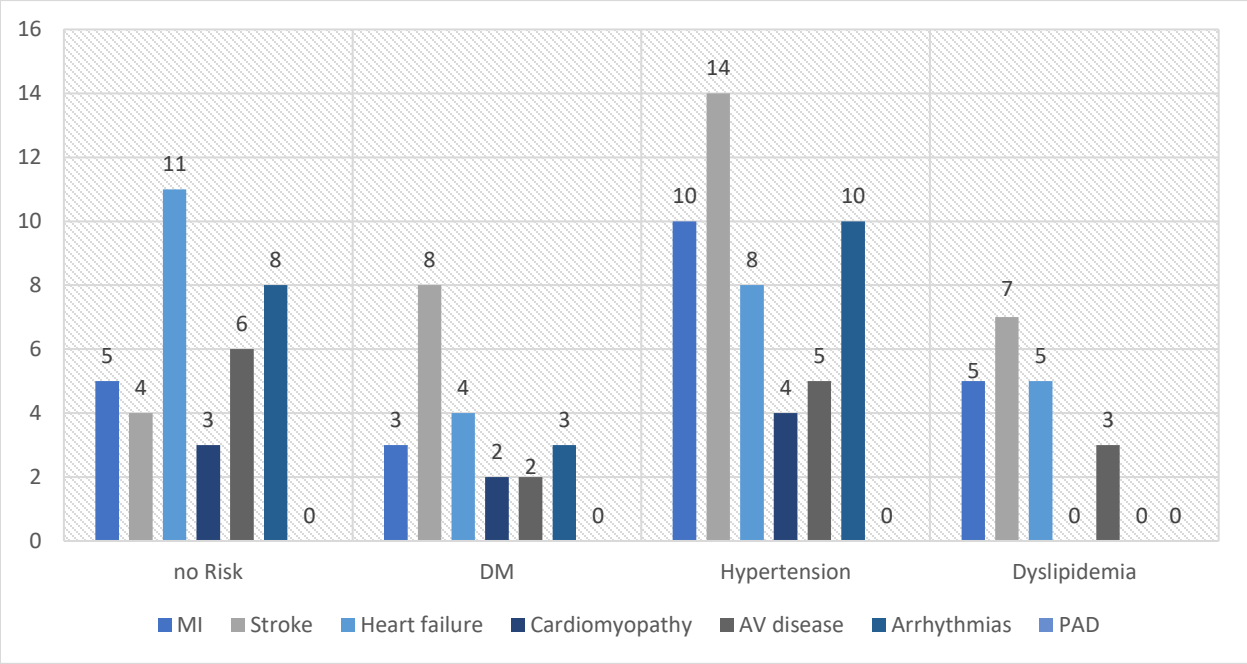

Figure 2: Comparison of Cardiovascular Disease in AS patients with or without Atherosclerosis Risk Diseases.

The mean age was 51 years, 74% were male. The respective highest prevalence of CVD and atherosclerosis risk disease was HF (2.9%) and HT (23%).

The impact of atherosclerosis risk disease and cardiovascular disease in Ankylosing spondylitis patients is shown in **Table 2.** For all 7 cardiovascular diseases, AS patients without DM HT or DLD have a lower prevalence of cardiovascular diseases. Whereas AS patients with atherosclerosis risk disease tend to increase the prevalence of cardiovascular disease; Patients with HT and DLD were increased risk of MI with OR 8.07 (95%CI 2.68-24.34), HT, DM, and DLD were increased risk of stroke with OR 12.10 (95%CI 4.01-36.55), HT, DM, and DLD were increased risk of heart failure with OR 5.18 (95%CI 1.427-18.814), DLD alone increased risk of HF with OR 3.68 (95%CI 1.31-10.36), HT and DLD increased risk of aortic valve disease with OR 6.37 (95%CI 1.63-24.88), and HT increased risk of cardiac arrhythmias with OR 3.80 (95%CI 1.52-9.50)

Table 2: The impact of atherosclerosis risk disease and cardiovascular disease in Ankylosing spondyloarthritis patients

CVD risk disease	Myocardial infarction		Odd ratio	p-value	95% CI
	Yes (16)	No (750)			
DM	3	77	2.017	0.272	0.562-7.235
HT	10	169	5.730	<0.001	2.053-15.994
DLD	5	55	5.744	<0.001	1.927-17.121
DM and HT	2	54	1.841	0.420	0.408-8.312
DM and DLD	1	29	1.657	0.627	0.212-12.978
HT and DLD	5	40	8.068	<0.001	2.675-24.337
DM HT and DLD	1	24	2.017	0.497	0.256-15.897
No risk disease	5	548	0.168	<0.001	0.058-0.488
	Stroke		Odd ratio	p-value	95% CI
	Yes (20)	No (746)			
DM	8	72	6.241	<0.001	2.470-15.770

HT	14	165	8.216	<0.001	3.109-21.714
DLD	7	53	7.041	<0.001	2.695-18.395
DM and HT	7	49	7.659	<0.001	2.923-20.072
DM and DLD	5	25	9.613	<0.001	3.239-28.531
HT and DLD	6	39	7.769	<0.001	2.832-21.315
DM HT and DLD	5	20	12.100	<0.001	4.006-36.545
No risk disease	4	549	0.090	<0.001	0.030-0.272
	Heart failure		**Odd ratio**	**p-value**	**95% CI**
	Yes (22)	**No (744)**			
DM	4	76	1.953	0.229	0.644-5.921
HT	8	171	1.915	0.144	0.790-4.641
DLD	5	55	3.684	0.008	1.310-10.364
DM and HT	3	53	2.059	0.247	0.590-7.180
DM and DLD	3	27	4.193	0.017	1.170-15.033
HT and DLD	3	42	2.639	0.116	0.751-9.274
DM HT and DLD	3	22	5.182	0.005	1.427-18.814
No risk disease	11	542	0.373	0.018	0.159-0.873
	Cardiomyopathy		**Odd ratio**	**p-value**	**95% CI**
	Yes (8)	**No (758)**			
DM	2	78	2.906	0.176	0.577-14.646
HT	4	175	3.331	0.074	0.825-13.458
DLD	0	60	NA	NA	NA
DM and HT	1	55	1.826	0.571	0.221-15.109
DM and DLD	0	30	NA	NA	NA
HT and DLD	0	45	NA	NA	NA
DM and HT and DLD	0	25	NA	NA	NA
No risk disease	3	550	0.227	0.028	0.054-0.958
	Aortic valve disease		**Odd ratio**	**p-value**	**95% CI**
	Yes (11)	**No (755)**			
DM	2	78	1.929	0.398	0.409-9.087
HT	5	174	2.783	0.081	0.839-9.228
DLD	3	57	4.592	0.016	1.186-17.786
DM and HT	2	54	2.885	0.163	0.068-13.687
DM and DLD	0	30	NA	NA	NA
HT and DLD	3	42	6.366	0.002	1.629-24.876
DM and HT and DLD	0	25	NA	NA	NA
No risk disease	6	547	0.456	0.188	0.138-1.511
	Arrhythmias		**Odd ratio**	**p-value**	**95% CI**
	Yes (19)	**No (747)**			
DM	3	77	1.631	0.440	0.465-5.726
HT	10	169	3.800	0.002	1.519-9.504
DLD	0	60	NA	NA	NA
DM and HT	2	54	1.510	0.586	0.340-6.707
DM and DLD	0	30	NA	NA	NA
HT and DLD	0	45	NA	NA	NA
DM and HT and DLD	0	25	NA	NA	NA
No risk disease	8	545	0.270	0.003	0.107-0.680

Discussion

The study found the prevalence of cardiovascular disease in AS except PAD. The prevalence of cardiovascular disease in AS patients including MI, stroke, heart failure, cardiomyopathy, aortic valve disease, and arrhythmia was 2.09, 2.61, 2.87, 1.04, 1.44, and 2.48% respectively. Unlike psoriatic arthritis(7,8), the association between AS and cardiovascular disease has remained controversial. (9) We perform what we believe to be the first nationwide Thailand healthcare database study on cardiovascular

disease and AS. The respective highest prevalence of CVD and atherosclerosis risk disease were HF and HT. In comparison with the fifth Thai Population Survey, 2014, which shows the prevalence of HT was 24.7% and DM was 8.9%, the prevalence of atherosclerosis risk disease was consistent with general populations.

The atherosclerosis risk factors are associated with CVD in AS patients, these results show compelling evidence that AS patients with atherosclerosis risk disease had a significant increase in Stroke, MI, aortic valve disease, arrhythmias, and HF when compared to the patients without risk factors.

Stroke, MI, and HF are three major cardiovascular outcomes and major vascular morbidity. In this study, a significant increase in Stroke, MI, and HF is consistent with the previous study. (10–12) We explain that the chronic inflammatory state in AS leading to enhanced atherosclerosis risk disease could contribute to endothelial damage and accelerated atherosclerosis. This result indicates that clinicians should consider the early diagnosis, treatment, and well control of atherosclerosis risk disease along with AS treatment.

The prevalence of cardiomyopathy was 1.04%. However, the prevalence might be underestimated because myocardial dysfunction can be asymptomatic for many years before having heart failure. The heart and aortic stiffness in AS patients was documented in the study of Moyssakis(13). Heslinga also reported an increased risk of diastolic LV dysfunction in AS(14), however, this study could not identify the prevalence of LV dysfunction.

A significant increase in aortic valve disease and arrhythmias is consistent with previous studies(15) and shows a non-significant increased rate of aortic regurgitation and conduction abnormalities compared to the normal population. However, our study can't identify specific aortic valve diseases and arrhythmias. To confirm these results, a large prospective study with patients with AS and with a matched control group should be performed in the future.

The strengths of our study include a nationwide Thailand healthcare database. However, the research findings have limitations. First, we lack information on the clinical risk factors such as smoking status, alcohol consumption, dietary habits, and amount of exercise, all of which could influence cardiovascular disease. Second, we lack information on the current treatment and the severity of AS. Third, the data doesn't include the out-patient database so it may not identify the overall impact of AS for CVD. Fourthly, the database consisted of individual records from the local hospital, without undergoing any data validation procedures.

In conclusion, The prevalence of cardiovascular disease and atherosclerosis risk disease are not increasing in AS patients. The presence of atherosclerosis risk disease consistently increases the risk of cardiovascular disease.

Reference

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007 Apr 21;369(9570):1379-1390. doi: 10.1016/S0140-6736(07)60635-7. PMID: 17448825.
2. Mathieu S, Pereira B, Soubrier M. Cardiovascular events in ankylosing spondylitis: an updated meta-analysis. Semin Arthritis Rheum. 2015 Apr;44(5):551-555. doi: 10.1016/j.semarthrit.2014.10.007. Epub 2014 Oct 18. PMID: 25455683.
3. Mathieu S, Soubrier M. Cardiovascular events in ankylosing spondylitis: a 2018 meta-analysis. Ann Rheum Dis. 2019 Jun;78(6):e57. doi: 10.1136/annrheumdis-2018-213317. Epub 2018 Mar 9. PMID: 29523520.
4. Bengtsson K, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. 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 Apr;77(4):541-548. doi: 10.1136/annrheumdis-2017-212189. Epub 2017 Dec 19. PMID: 29259045.
5. Ozkan Y. Cardiac Involvement in Ankylosing Spondylitis. J Clin Med Res. 2016 Jun;8(6):427-30. doi: 10.14740/jocmr2488w. Epub 2016 May 25. PMID: 27222669; PMCID: PMC4852774.
6. Aviña-Zubieta JA, Chan J, De Vera M, Sayre EC, Choi H, Esdaile J. Risk of venous thromboembolism in ankylosing spondylitis: a general population-based study. Ann Rheum Dis.

2019 Apr;78(4):480-485. doi: 10.1136/annrheumdis-2018-214388. Epub 2019 Feb 8. PMID: 30737222.

7. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, Jullien D, Aractingi S, Aubin F, Joly P, Le Maître M, Ortonne JP, Paul C, Richard MA. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol. 2013 Aug;27 Suppl 3:12-29. doi: 10.1111/jdv.12163. PMID: 23845149.
8. Peluso R, Caso F, Tasso M, Ambrosino P, Dario Di Minno MN, Lupoli R, Criscuolo L, Caso P, Ursini F, Puente AD, Scarpa R, Costa On Behalf Of CaRRDs Study Group L. Cardiovascular Risk Markers and Major Adverse Cardiovascular Events in Psoriatic Arthritis Patients. Rev Recent Clin Trials. 2018;13(3):199-209. doi: 10.2174/1574887113666180314105511. PMID: 29542417; PMCID: PMC6691775.
9. Arida A, Protogerou AD, Konstantonis G, Konsta M, Delicha EM, Kitas GD, Sfikakis PP. Subclinical Atherosclerosis Is Not Accelerated in Patients with Ankylosing Spondylitis with Low Disease Activity: New Data and Metaanalysis of Published Studies. J Rheumatol. 2015 Nov;42(11):2098-105. doi: 10.3899/jrheum.150316. Epub 2015 Oct 1. PMID: 26428207.
10. Haroon NN, Paterson JM, Li P, Inman RD, Haroon N. Patients With Ankylosing Spondylitis Have Increased Cardiovascular and Cerebrovascular Mortality: A Population-Based Study. Ann Intern Med. 2015 Sep 15;163(6):409-16. doi: 10.7326/M14-2470. PMID: 26258401.
11. Zhao SS, Robertson S, Reich T, Harrison NL, Moots RJ, Goodson NJ. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. Rheumatology (Oxford). 2020 Oct 1;59(Suppl4):iv47-iv57. doi: 10.1093/rheumatology/keaa246. PMID: 33053193; PMCID: PMC7566561.
12. Essers I, Stolwijk C, Boonen A, De Bruin ML, Bazelier MT, de Vries F, van Tubergen A. Ankylosing spondylitis and risk of ischaemic heart disease: a population-based cohort study. Ann Rheum Dis. 2016 Jan;75(1):203-9. doi: 10.1136/annrheumdis-2014-206147. Epub 2014 Oct 31. PMID: 25362044.
13. Moyssakis I, Gialafos E, Vassiliou VA, Boki K, Votteas V, Sfikakis PP, Tzelepis GE. Myocardial performance and aortic elasticity are impaired in patients with ankylosing spondylitis. Scand J Rheumatol. 2009 May-Jun;38(3):216-21. doi: 10.1080/03009740802474672. PMID: 19229673.
14. Heslinga SC, Van Dongen CJ, Konings TC, Peters MJ, Van der Horst-Bruinsma IE, Smulders YM, Nurmohamed MT. Diastolic left ventricular dysfunction in ankylosing spondylitis--a systematic review and meta-analysis. Semin Arthritis Rheum. 2014 Aug;44(1):14-9. doi: 10.1016/j.semarthrit.2014.02.004. Epub 2014 Feb 14. PMID: 24655534.
15. 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 Feb;25(1):24-9. doi: 10.1007/s10067-005-1117-6. Epub 2005 Oct 25. PMID: 16247583.