Research Square

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No Increased Risk of Alopecia in Ankylosing Spondylitis Patients: A Population-based Cohort Study in Taiwan

Jason Peijer Hsieh
Taipei Veterans General Hospital
Hsi-Kai Tsou
Taichung Veterans General Hospital
Yung-Heng Lee
Miaoli General Hospital
Yu-Hsun Wang
Chung Shan Medical University Hospital
James Cheng-Chung Wei (jccwei@gmail.com)
Chung Shan Medical University Hospital

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Abstract

Background: Investigate the association between AS and alopecia.

Methods: Using over 1,000,000 patients' data from Taiwan Longitudinal Health Insurance Database, we selected the sample with ICD code, diagnosing date, index date, and propensity score matching. We had 3,640 patients with AS and 14,560 non-AS controls. Cox proportional hazard model and Kaplan-Meier analysis were used to present the results.

Results: The crude and adjusted hazard ratio of AS for developing alopecia showed no statistical significance in the Cox proportional hazard model [crude hazard ratio (HR) 1.16, 95% CI 0.67-1.99; adjusted HR 1.16, 95% CI 0.67-1.98]. Negative results were found as well in subgroup analysis (Age 20-40: HR 1.03, 95% CI 0.53-2.01; Age≧40: HR 1.49, 95% CI 0.58-3.80; Female: HR 1.17, 95% CI 0.43-3.17; Male: HR 1.15, 95% CI 0.61-2.19). A significant positive correlation was found between atopic dermatitis and alopecia (adjusted HR 8.05, 95% CI 1.11-58.14).

Conclusions: No increased risk of alopecia was observed in AS patients

Background

Ankylosing spondylitis (AS) is one of the spondyloarthritis (SpA) family, in which the disorders may share common manifestation, including axial inflammatory arthritis, enthesitis, dactylitis, peripheral arthritis, and certain extra-auricular disorders. Among SpA, AS is the most common[1]. AS showed a male predominance, with a 3:1 male/female ratio. The androgen level in AS patients remains controversial[2]. Alopecia may be genetic, psychogenic, androgenetic, autoimmune[3-5], iatrogenic, idiopathic, etc. It can be limited over the forehead, be patchy, or extends to whole body hair loss. Generally, alopecia happens more in men, especially androgenetic alopecia. It is unclear if AS correlates with alopecia since both disorders are predominant in men. Moreover, previous studies showed autoimmunity and certain autoimmune diseases are related to alopecia, such as systemic lupus erythematosus, vitiligo, Hashimoto's thyroiditis, and so on[6-10]. However, to date, the association between AS and alopecia remains unanswered. Thus, this study was designed and aimed to clarify the relationship between AS and alopecia.

Patients And Methods

Data source

We did a retrospective cohort study from claim-based data of 1 million population in Taiwan Longitudinal Health Insurance Database (LHID). This national database comprises medical information, such as diagnosed diseases, drug history, as well as other details of more than 99% of the population in Taiwan. These medical profiles can be used for study or other purposes. The patients' data were shown anonymously in the form of codes and numbers, which enhance the randomization of the study and the

patients' privacy. Finally, this study was approved by the Ethics Review Board of Chung Shan Medical University.

Study cohort and controls

We selected newly diagnosed (outpatient department visit ≥ 3 times or admission ≥ 1 time) patients with AS (ICD-9-CM=720.0) from 2000-2012. Patients under 20 years old, and patients diagnosed with alopecia (ICD-9-CM=704.0) before the index date (The date of AS diagnosis) were excluded. The patients were followed until they were diagnosed with alopecia or until Dec 31, 2013. For the non-AS comparison group, we chose the patients without diagnoses of AS during 1999-2013. Two groups were matched 1:8 by age and gender, and then these two groups were matched 1:4 with propensity score by hypertension (ICD-9-CM=401-405), hyperlipidemia (ICD-9-CM=272.0-272.4), diabetes (ICD-9-CM=250), atopic dermatitis (ICD-9-CM=691), thyroid diseases (ICD-9-CM=240-246), mental disorders (ICD-9-CM=290-319), cancer (ICD-9-CM=140-208), and autoimmune diseases [RA (ICD-9-CM codes=714.0) and SLE (ICD-9-CM codes=710.0)]. Finally, we got an AS group with 3,640 patients and 14,560 non-AS controls. Figure 1 shows the sample-selecting flowchart. The primary endpoint was alopecia, defined by ICD-9 coding 704.0.

Statistical analysis

We compared the demographic characteristics of the two groups by using the test and the Student's t-test for categorical and continuous variables respectively. The development of alopecia as time passed between the two groups was depicted by Kaplan-Meier analysis. Cox proportional hazard model was used to assess the hazard ratio (HR) of developing alopecia in all patients.

Results

The baseline characteristics of the two groups were comparable after matching. Table 1 shows the demographic characteristics of the AS group and the non-AS group.

Table 1. Demographic characteristics of Ankylosing Spondylitis and Non-Ankylosing Spondylitis

	Before propensity score matched					After propensity score matched				
	AS (N =3715)		Non-AS (N =29720)			AS (N =3640)		Non-AS (N =14560)		
	n	%	N	%	p-value	n	%	n	%	p-value
Age					1					0.804
20-40	1571	42.3	12568	42.3		1548	42.5	6146	42.2	
40-65	1530	41.2	12240	41.2		1488	40.9	5932	40.7	
≧65	614	16.5	4912	16.5		604	16.6	2482	17.0	
Mean ± SD	45.8 ± 16.9		45.8 ± 16.9		1	45.7 ± 17		46.1 ± 17.1		0.278
Gender					1					0.693
Female	1474	39.7	11792	39.7		1426	39.2	5756	39.5	
Male	2241	60.3	17928	60.3		2214	60.8	8804	60.5	
Hypertension	623	16.8	3777	12.7	**<0.001**	602	16.5	2423	16.6	0.881
Hyperlipidemia	203	5.5	1268	4.3	**0.001**	200	5.5	809	5.6	0.884
Diabetes	258	6.9	1836	6.2	0.069	252	6.9	1028	7.1	0.772
Atopic dermatitis	12	0.3	70	0.2	0.309	11	0.3	34	0.2	0.455
Thyroid disease	56	1.5	306	1.0	**0.008**	54	1.5	240	1.6	0.480
Mental disorder	412	11.1	1813	6.1	**<0.001**	398	10.9	1571	10.8	0.802
Cancer	71	1.9	452	1.5	0.071	68	1.9	263	1.8	0.803
Autoimmune disease	79	2.1	86	0.3	**<0.001**	8	0.2	32	0.2	1

Legends: AS- Ankylosing spondylitis. N- Number of total patients. n- Number of patients in defferent categories. SD- Standard Deviation.

The risk of developing alopecia was assessed in all patients, and the crude and adjusted HR of AS showed no statistical significance (crude HR 1.16, 95% CI 0.67-1.99; adjusted HR 1.16, 95% CI 0.67-1.98). The adjusted HR was adjusted for age, gender, hypertension, hyperlipidemia, diabetes, atopic dermatitis, and mental disorder. Among all the characteristics, age over 40 has a negative correlation with alopecia (Crude HR 0.33, 95% CI 0.20-0.55, adjusted HR 0.35, 95% CI 0.20-0.61). Moreover, patients with atopic dermatitis were associated with a higher risk of alopecia (adjusted HR 8.05, 95% CI 1.11-58.14). Other comorbidities showed no significant correlation with alopecia. Table 2 showed the Cox proportional hazard model of all patients in incidental alopecia. We further analyzed the HR of alopecia areata and universalis, which were also non-significant.

Table 2. Cox proportional hazard model. Bold font represents statistical significance (p< 0.05).

	No. of Alopecia areata	Observed P-Y	Incidence Density (Per 1000P-Y)	Crude HR	95% C.I.	Adjusted HR†	95% C.I.
Ankylosing Spondylitis							
No	58	113418	0.5	1		1	
Yes	17	28731	0.6	1.16	0.67-1.99	1.16	0.67-1.98
Age							
20-40	53	63568	0.8	1		1	
≧40	22	78581	0.3	**0.33**	**0.2-0.55**	**0.35**	**0.20-0.61**
Gender							
Female	22	55092	0.4	1		1	
Male	53	87057	0.6	1.53	0.93-2.51	1.18	0.71-1.96
Hypertension	8	20266	0.4	0.71	0.34-1.48	1.52	0.64-3.58
Hyperlipidemia	3	6427	0.5	0.87	0.27-2.75	1.51	0.43-5.24
Diabetes	1	8100	0.1	0.22	0.03-1.58	0.29	0.04-2.25
Atopic dermatitis	1	287	3.5	6.55	0.91-47.13	**8.05**	**1.11-58.14**
Mental disorder	2	14096	0.1	0.25	0.06-1.01	0.32	0.08-1.32

Legends: No.- Number. P-Y- Person-Years. HR- Hazard ratio. Cross mark (†) - Adjusted for age, gender, hypertension, hyperlipidemia, diabetes, atopic dermatitis, and mental disorder. C.I.- Confidence interval.

A subgroup analysis of the Cox proportional hazard model was done to clarify the risk of developing alopecia in AS patients, and the result showed no statistical significance. Table 3 displays the subgroup analysis of the Cox proportional hazard model.

Table 3. Subgroup analysis of Cox proportional hazard model

	AS		Non-AS			
	N	No. of Alopecia areata	N	No. of Alopecia areata	HR	95% CI
Age						
20-40	1548	11	6146	42	1.03	0.53-2.01
≧40	2092	6	8414	16	1.49	0.58-3.80
Gender						
Female	1426	5	5756	17	1.17	0.43-3.17
Male	2214	12	8804	41	1.15	0.61-2.19

Legends: AS- Ankylosing spondylitis. N- Number of patients. No.- Number. HR- Hazard ratio. C.I.- Confidence interval.

Figure 2 showed the Kaplan-Meier analysis of AS and non-AS patients. The results revealed no significant difference in developing alopecia during follow-up for up to 14 years. (p=0.595).

Discussion

In this nationwide population-based cohort study, the results suggested that AS patients have no increased risk of alopecia compared to healthy individuals.

Though it is clear that androgens have an impact on modulating our immunity, the androgen level in AS patients remain controversial[2]. Few recent studies showed no elevation of androgen in patients with AS[11-14]. A study by Gracey et al. in recent years displayed an elevated frequency of T-helper 17 (Th17) cells and interleukin (IL)-17A in male AS patients instead of female AS patients[14]. This changed Th17 axis may be the key to increased incidence of AS in males, and no different level in sex hormone was examined between AS and healthy individuals. This conclusion may indicate less correlation between AS and alopecia, especially androgenetic alopecia.

A clear positive relationship between atopic dermatitis (AD) and alopecia was noticed. AD may be associated with alopecia, which was reported in previous studies[7, 15-17]. Mohan et al. mentioned possible common pathways in AD and alopecia areata, including thymic stromal lymphopoietin, Th17, or filaggrin gene mutations[16]. No association between alopecia and other comorbidities such as hypertension, hyperlipidemia, diabetes, and mental disorders was seen in the Cox proportional hazard model.

AS patients have more exposure to tumor necrosis factor-alpha (TNFa) inhibitors, some of which had been reported to cause hair loss[18]. However, only few kinds of TNFa inhibitors had been listed and only few cases were recorded. This indicates a low incidence of alopecia while using TNFa inhibitors, and statistical significance may not be reached under this situation. TNFa might have a positive effect on hair growth [19]. Adalimumab, infliximab, etanercept, and several TNFa inhibitors have been reported to cause alopecia, including alopecia areata and alopecia universalis, when used in autoimmune diseases[18, 20-25]. Further studies with a stronger level of evidence are needed to confirm an epidemiological association between TNFa inhibitor and all kinds of hair loss.

Elevation of certain cytokine levels in circulation was observed in AS patients, such as IL-12, IL-17, and IL-23[26-31]. Also, elevation in IL-12 and IL-23 was noted in patients with alopecia areata[4, 5, 32]. Though the increase in circulatory cytokine level has something to do with one's systemic inflammatory response and overall immunity, this may not imply a direct association between AS and alopecia. To date, no adequate evidence supports a higher risk of alopecia in AS patients due to systemically increased inflammatory reaction.

The limitations of this study include that the 14-year follow-up time might not be enough to develop androgenetic alopecia in AS patients. The onset of AS is mostly at a young age[33], while most androgenic alopecia develops at the age of at least 30[34]. However, this is only regarding androgenetic alopecia. For alopecia areata, it mostly occurs in younger individuals. We analyzed the HR of alopecia areata and universalis, which were statistically non-significant as well. Second, patients of androgenetic alopecia might not seek medical help in this dataset, causing under-diagnosis of the endpoint. This explains the protective correlation between age greater than 40 and alopecia in our Cox proportional hazard model (table 2). Nevertheless, due to the higher medical demand of alopecia among young patients, this correlation between age greater than 40 and alopecia seemed reasonable.

This study had several strengths. First, the data was from LHID, which covered a population of 1 million in Taiwan. The sample size was great enough for giving strong evidence between AS and alopecia. Moreover, we comprehensively matched the demographic characteristics of the two groups. Last, this is so far the first nationwide and population-based study on the relationship between AS and alopecia.

Conclusions

In conclusion, AS patients were not associated with a higher risk of alopecia. These data could reduce concerns among healthcare providers about managing patients with AS.

List Of Abbrevations

Hazard ratio (HR), ankylosing spondylitis (AS), spondyloarthritis (SpA), longitudinal Health Insurance Database (LHID), T-helper (Th), interleukin (IL), atopic dermatitis (AD), tumor necrosis factor-alpha (TNFa), standard Deviation (SD), number (No.), Person-Years (P-Y), confidence interval (C.I.)

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Review Board of Chung Shan Medical University.

Consent for publication: Not applicable.

Availability of data and materials: The data that support the findings of this study are available from Taiwan Longitudinal Health Insurance Database but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Taiwan Longitudinal Health Insurance Database.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

Hsieh was a major contributor in writing the manuscript. Tsou and Lee have substantively revised the work. Wang analyzed and interpreted the patient data. Wei have made substantial contributions to the conception of the work.

All authors read and approved the final manuscript.

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Figures

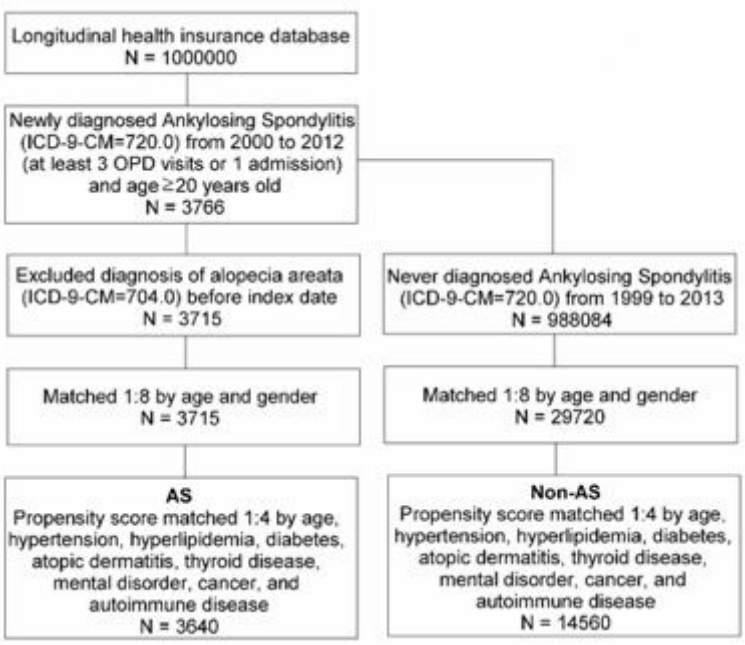

Figure 1

Flow chart of patient selection. Legends: N- Number of patients. OPD- Outpatient department. ADM- Admission. AS- Ankylosing spondylitis

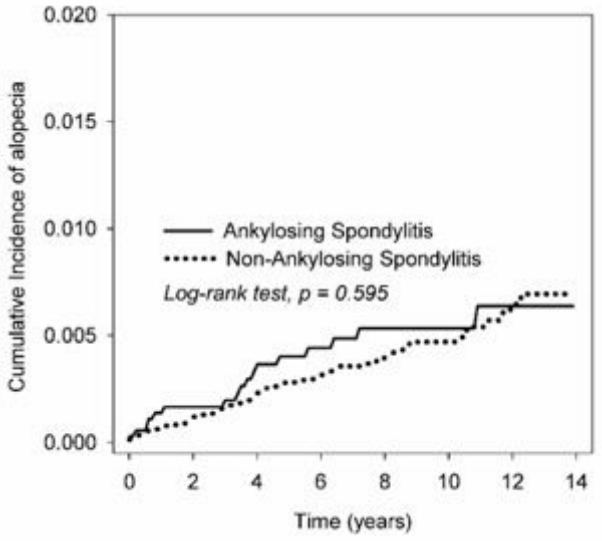

Figure 2

Kaplan-Meier analysis of AS and non-AS patients.