


CLINICAL ARTICLE

Gender Differences in Ankylosing Spondylitis Patients with Advanced Hip Involvement: Results from A Matched Retrospective Cohort Study

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Objective: To determine the gender differences in ankylosing spondylitis (AS) patients with advanced hip involvement.

Methods: We retrospectively analyzed the 373 consecutive AS patients with advanced hip involvement from 2012 to 2017 and divided them into two groups by sex with 340 men and 33 women. Research data on hip involvement in the patients were obtained from medical records and radiographs. The severity of radiographic hip involvement was evaluated by the Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip) scoring system. The data on clinical characteristics, radiographic hip involvement, and laboratory values were compared between the two groups. The comparison was performed again between the two groups after adjusting for the onset age and disease duration by propensity score matching (PSM).

Results: Men underwent total hip arthroplasty earlier than women in the patients, with a median age of 31 years (range, 19–67 years) vs 36 years (range, 23–67 years), respectively ($P < 0.05$). Hip involvement was found to be younger in men than that in women, with a median age of 18 years (range, 7–56 years) vs 23 years (range, 5–55 years) ($P < 0.05$), and men with bilateral onset in hips had a higher frequency than women with that (66.2% vs 39.4%) ($P < 0.05$). There was no gender difference in the proportion of bilateral advanced hip involvement (85.3% vs 72.7%) ($P > 0.05$). The proportion of the patients who had spinal involvement (89.1% vs 69.7%), flexion contracture in the hip (43.8% vs 24.2%), hip range of motion = 0° (53.5% vs 30.3%), and an elevated level of C-reactive protein (CRP) (69.1% vs 51.5%) was significantly higher in men than that in women ($P < 0.05$). After adjusting for the onset age and disease duration by PSM (1:1), men with bilateral onset in hips still had a higher frequency than women with that (76.7% vs 40.0%), and the proportion of the patients who had spinal involvement (90.0% vs 66.7%) and an elevated level of CRP (80.0% vs 53.3%) was significantly higher in men than that in women ($P < 0.05$).

Conclusions: The disease pattern of hip involvement in AS has gender differences, with bilateral onset being the dominant pattern in men and unilateral onset being more common in women. However, the frequency of bilateral advanced hip involvement has no gender difference eventually. The higher prevalence of spinal involvement in men with AS may be responsible for the more severe functional impairment compared with women.

Key words: Ankylosing spondylitis; Disease pattern; Functional impairment; Gender difference; Hip involvement

Introduction

Ankylosing spondylitis (AS) is a chronic autoimmune disease characterized by mainly affecting sacroiliac joint

and spine, and peripheral joints and extra-articular structures may also be affected^{1,2}. Men make up the majority of the cohort being affected by AS with a ratio of men *versus*

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women approximately (2–3) : 1^{3–5}. Also, the disease pattern of AS has gender differences, which have been shown in inheritance, age at onset, spinal involvement, peripheral joints involvement, radiographic damage, and functional impairment *et al.*^{4–13}. For quite a long period of time, the diagnostic delay persisted in female AS patients due to the continuing bias of AS being a disease of only men or differences in the disease expression in women⁴. However, with the deepening understanding of gender differences in the disease, the delay in diagnosis may now tend to be equivalent between men and women. Studies in recent years have shown that the delay in diagnosis of AS in women is only slightly later than that in men^{7,8,14} or not different from that in men^{5,9}. Meanwhile, several studies have found that men with AS are significantly younger at disease onset and experience longer disease duration than women with that^{5,7,9,15}, while some other studies have not^{8,14}.

There are other gender differences in the disease pattern of AS. Previous studies have consistently shown that men tend to have more thoracic and lumbar spinal radiographic severity^{3,4,11}. Oppositely, women tend to have less structural damage in both the sacroiliac joints and the spine¹⁶ and to have more common radiographic progression in the cervical vertebrae^{3,17}. Wright *et al.* believed that this lower prevalence of definitive sacroiliitis or spinal radiographic progression in women than in men was considered to be one reason contributing to the predominance of men in AS¹⁷. Additionally, both early and recent findings have revealed that men with AS have more severe spinal radiographic damage than women, regardless of the measurement being performed by the Bath Ankylosing Spondylitis Functional Index (BASFI)^{8,13,18} or by the modified Stoke AS Spine Score (mSASSS)¹⁹. However, the gender-attributable differences in disease activity or functional impairment are still controversial in previously reported literature^{4,5,8–10,12–14,17,20,21}. Commonly, there is a paucity of data on hip involvement being included in these previous studies.

Hip involvement is a particular concern in AS and commonly leads to severe functional impairment in the patients^{22,23}. Moreover, the combination of stiffness or ankylosis in the spine and hip can cause restricted body functions and disabilities in AS patients, which not only affects the physical status, employability, psychosocial status, and comprehensive quality of life in the patients but also leads to socioeconomic burdens^{24–28}. The previously reported prevalence of hip involvement in AS patients varies from 9% to 38%, with bilateral involvement being more common^{22,29–32}. Vander Cruyssen *et al.* considered this wide range in the prevalence could be explained by the different definitions that are used to describe the investigated population and by different definitions of hip involvement²³. Traditionally, hip involvement in AS can be described as clinical hip involvement, radiological hip involvement, or the need for hip replacement surgery, which are respectively based on the rheumatologist's clinical perception, the Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip) scoring

system³³, or the presence of one or two replaced hips³⁰. Until now, the BASRI-hip scoring system is the most commonly used instrument for assessing radiographic hip involvement in AS. Based on this, several studies have shown that patients with hip involvement tend to have worse BASFI scores than those without hip involvement, regardless of being clinical or radiological hip involvement^{29,30,34–36}. Vander Cruyssen *et al.* have proposed two possible explanations, one of which is that some questions in the BASFI scoring system appear to be directly related to the hip, and the other of which is that hip involvement is associated with more severe axial disease in terms of ankylosis progression³⁰. Moreover, Ward *et al.* found that the association of hip arthritis and functional limitations was independent of radiographic spinal damage, which suggests that hip arthritis has a more prominent role than spinal damage in functional limitations among patients with longstanding AS³⁴.

As noted above, the functional impairment has gender differences in AS patients, and hip involvement has been deemed to be a negative factor on the prognosis of AS or to be associated directly with functional limitations in AS patients^{30,34,35,37}. Therefore, we supposed that hip involvement might be one of the remarkable causes contributing to the differences. Additionally, some previous studies have shown the predominance of men in AS related hip involvement^{8,35,36,38}, but there has been no report concerning the association of gender differences and the severity of hip involvement. Also, clarifying the gender-attributable differences in AS patients with advanced hip involvement can contribute to a full understanding of the disease. Thus, the present study aimed to determine the gender differences in AS patients with advanced hip involvement, and surgeons should be aware of that before performing total hip arthroplasty (THA).

Materials and Methods

Subjects and Grouping Criteria

After obtaining the approval of the institutional review board of our hospital, the 405 consecutive AS patients with advanced hip involvement who were admitted to our department due to requiring hip replacement from January 2012 to December 2017 were included in this study. The diagnosis of AS followed the 1984 modified New York criteria³⁹, and the inclusion criteria were patients who had definite indications of THA due to their advanced hip involvement⁴⁰. The exclusion criteria were as follows: (i) those with a history of hip trauma or operation in hips (seven cases); (ii) spine and hip procedure being performed during the same admission (three cases); (iii) coagulation disorders that may cause hip arthritis (three cases); and (iv) incomplete or abnormal medical data (11 cases). Eventually, 373 AS patients with advanced hip involvement were enrolled in this retrospective cohort study. The patients were divided into two groups by sex with 340 men and 33 women to investigate the gender-attributable differences in AS patients with advanced hip involvement. Gender differences in clinical characteristics,

radiographic hip involvement, and laboratory values were compared between the two groups. The comparison was performed again between the two groups after adjusting for the onset age and disease duration by propensity score matching (PSM).

Research Data

Research data were obtained from medical records and radiographs. The clinical and laboratory data included age at surgery, body mass index (BMI), onset age of hip involvement (time of symptom onset in the hip), disease duration (time from onset to requiring THA), bilateral onset in hips (initial symptom occurred bilaterally in the hips), administration of tumor necrosis factor- α (TNF- α) inhibitors, family history of rheumatism, spinal involvement (determined by the combination of disease history, restricted spinal activity, and radiographs), bilateral advanced hip involvement (determined by requiring THA in both sides), flexion contracture in the hip, hip range of motion (ROM) = 0°, Harris hip score (only the involved hips were calculated), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. Elevated ESR and CRP levels were defined as follows in the patients: ESR >15 mm/1 h for men and > 20 mm/1 h for women and CRP >1 mg/dL.

Radiological Assessments

The severity of radiographic hip involvement was evaluated by the BASRI-hip scoring system³³, which is graded on a scale of 0–4 (0, no change; 1, suspicious: focal joint space narrowing; 2, mild: circumferential joint space narrowing >2 mm; 3, moderate: circumferential joint space narrowing \leq 2 mm or bone-on-bone apposition of <2 cm; 4, severe: bone deformity or bone-on-bone apposition of \geq 2 cm). The BASRI-hip was scored by two trained readers according to preoperative anteroposterior pelvic radiographs. If the score differed between the two readers, the final score was determined by another experienced senior surgeon.

Statistical Analysis

Continuous variables were presented as mean \pm standard deviation or median (minimum to maximum) and categorical variables were shown as frequency and percentage. The normally and non-normally distributed continuous variables were compared by the Student's *t*-test and Mann-Whitney *U* test, respectively. Categorical and dichotomous variables were compared by the Chi-square test or Fisher's exact test. A PSM method was used to adjust for the onset age and disease duration in hip involvement between the two groups. Differences were considered to be statistically significant at a *P* value of <0.05. Data analyses were performed with IBM SPSS statistics for windows, version 25.0 (IBM, Armonk, NY, USA).

Results

General Comparison between Gender

Men underwent THA earlier than women in the AS patients, with a median age of 31 years (range, 19–67 years) vs 36 years (range, 23–67 years), respectively (*P* < 0.05). Hip involvement was found to be younger in men than that in women, with a median age of 18 years (range, 7–56 years) vs 23 years (range, 5–55 years) (*P* < 0.05), and men had a higher frequency of bilateral onset in hips than women in the patient (66.2% vs 39.4%) (*P* < 0.05). There was no gender difference in the proportion of bilateral advanced hip involvement (85.3% vs 72.7%) (*P* > 0.05). The proportion of the patients who had spinal involvement (89.1% vs 69.7%), flexion contracture in the hip (43.8% vs 24.2%), and hip ROM = 0° (53.5% vs 30.3%) was significantly higher in men than that in women (*P* < 0.05). The proportion of using TNF- α inhibitors was lower in men than that in women (*P* < 0.05). No gender differences were observed in BMI, disease duration, family history of rheumatism, Harris hip score, ESR, CRP, and the distribution of grade in BASRI-hip (*P* > 0.05). However, the frequency of an elevated level of CRP (69.1% vs 51.5%) in men was higher than that in women (*P* < 0.05), while that of an elevated level of ESR (52.9% vs 45.5%) showed no significant difference between gender (*P* > 0.05, Table 1).

Comparison between Gender after Adjustment

After adjusting for the onset age and disease duration by PSM (1:1), men with bilateral onset in hips still had a higher frequency than women with that (76.7% vs 40.0%), and the proportion of the patients who had spinal involvement (90.0% vs 66.7%) was still significantly higher in men than that in women (*P* < 0.05). No gender differences were observed in age at admission, BMI, administration of TNF- α inhibitors, family history of rheumatism, the proportion of bilateral advanced hip involvement, the proportion of flexion contracture in the hip, the proportion of hip ROM = 0°, Harris hip score, ESR, CRP, and the distribution of grade in BASRI-hip (*P* > 0.05). Similarly, after adjustment, the frequency of an elevated level of CRP (80.0% vs 53.3%) in men remained higher than that in women (*P* < 0.05), while that of an elevated level of ESR (53.3% vs 46.7%) showed no significant difference between gender (*P* > 0.05) (Table 2).

Discussion

Gender Differences in the Disease Pattern of AS

Numerous studies have shown that the disease pattern of AS has gender differences^{3,5,7–12}. Hip involvement has been deemed to be more prevalent in men^{8,35,36,38} and to be a negative prognostic predictor for the severity of AS^{30,34,35,37}. Even so, it seems that men do not necessarily have worse functional impairment than women^{5,8–10,12,13}, which may be interpreted that the body parts being affected¹⁰ or the severity of the disease varies between gender. Therefore, we

TABLE 1 Comparison between men and women in AS patients with advanced hip involvement

Variables	Men (n = 340)	Women (n = 33)	t, Z, or χ^2	P
Clinical characteristics				
Age at surgery (years)	31 (19 to 67)	36 (23 to 67)	-2.292 [‡]	0.022 [*]
BMI(kg/m ²)	22.68 (11.87 to 41.62)	22.04 (15.63 to 36.73)	-0.509 [‡]	0.611
Onset age of hip involvement (years)	18 (7 to 56)	23 (5 to 55)	-3.185 [‡]	0.001 [*]
Disease duration (years)	10.9 (0.5 to 40.3)	8 (1 to 40)	-1.062 [‡]	0.288
Bilateral onset in hips (n, %)	225 (66.2%)	13(39.4%)	9.343 [§]	0.002 [*]
Administration of TNF- α inhibitors (n, %)	28 (8.2%)	8 (24.2%)	8.839 [§]	0.003 [*]
Family history of rheumatism (n, %)	34 (10.0%)	5 (15.2%)	0.853 [§]	0.356
Spinal involvement (n, %)	303 (89.1%)	23 (69.7%)	10.302 [§]	0.001 [*]
Bilateral advanced hip involvement (n, %)	290 (85.3%)	24 (72.7%)	3.568 [§]	0.059
Flexion contracture in the hip (n, %)	149 (43.8%)	8 (24.2%)	4.732 [§]	0.030 [*]
Hip ROM = 0° (n, %)	182 (53.5%)	10 (30.3%)	6.497 [§]	0.011 [*]
Harris hip score	37.50 \pm 19.88	43.22 \pm 16.58	-1.745 [†]	0.082
Radiographic hip involvement (No. of hip cases with a BASRI-hip score of 0-4)			9.410 [§]	0.052
0 (n, %)	16 (2.4%)	4 (6.1%)		
1 (n, %)	34 (5.0%)	5 (7.6%)		
2 (n, %)	31 (4.5%)	6 (9.1%)		
3 (n, %)	283 (41.6%)	30 (45.4%)		
4 (n, %)	316 (46.5%)	21 (31.8%)		
Laboratory values				
ESR (mm/1 h)	16 (1 to 108)	14 (4 to 97)	-1.707 [‡]	0.088
Elevated level of ESR (n, %)	180 (52.9%)	15 (45.5%)	0.676 [§]	0.411
CRP (mg/dL)	1.65 (0.10 to 17.87)	1.22 (0.10 to 9.76)	-1.640 [‡]	0.101
Elevated level of CRP (n, %)	235 (69.1%)	17 (51.5%)	4.253 [§]	0.039 [*]

The continuous variables are presented as mean \pm standard deviation or median (minimum to maximum). †, ‡, and § represent t, Z, and χ^2 value, respectively; *P < 0.05 represents having statistically significance. AS, ankylosing spondylitis; BASRI-hip, Bath Ankylosing Spondylitis Radiology Hip Index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ROM, range of motion; TNF- α , tumor necrosis factor- α .

TABLE 2 Comparison between men and women after adjusting for the onset age and disease duration by PSM

Variables	Men (n = 30)	Women (n = 30)	t, Z, or χ^2	P
Clinical characteristics				
Age at surgery (years)	31 (19 to 67)	36 (23 to 67)	-0.829 [‡]	0.407
BMI (kg/m ²)	22.68 (11.87 to 41.62)	22.04 (15.63 to 36.73)	-1.050 [‡]	0.294
Bilateral onset in hips (n, %)	23 (76.7%)	12 (40.0%)	8.297 [§]	0.004 [*]
Administration of TNF- α inhibitors (n, %)	5 (16.7%)	7 (23.3%)	0.417 [§]	0.519
Family history of rheumatism (n, %)	4 (13.3%)	5 (16.7%)	0.131 [§]	0.718
Spinal involvement (n, %)	27 (90.0%)	20 (66.7%)	4.812 [§]	0.028 [*]
Bilateral advanced hip involvement (n, %)	25 (83.3%)	23 (76.7%)	0.417 [§]	0.519
Flexion contracture in the hip (n, %)	13 (43.3%)	8 (26.7%)	1.832 [§]	0.176
Hip ROM = 0° (n, %)	10 (33.3%)	9 (30.0%)	0.077 [§]	0.781
Harris hip score	43.74 \pm 15.67	40.59 \pm 18.49	0.787 [†]	0.434
Radiographic hip involvement (No. of hip cases with a BASRI-hip score of 0 ~ 4)			1.314 [§]	0.859
0 (n, %)	3 (5.0%)	3 (5.0%)		
1 (n, %)	2 (3.3%)	4 (6.7%)		
2 (n, %)	4 (6.7%)	6 (10.0%)		
3 (n, %)	30 (50.0%)	29 (48.3%)		
4 (n, %)	21 (35.0%)	18 (30.0%)		
Laboratory values				
ESR (mm/1 h)	16 (1 to 108)	14 (4 to 97)	-1.102 [‡]	0.270
Elevated level of ESR (n, %)	16 (53.3%)	14 (46.7%)	0.267 [§]	0.606
CRP (mg/dL)	1.65 (0.10 to 17.87)	1.22 (0.10 to 9.76)	-1.856 [‡]	0.063
Elevated level of CRP (n, %)	24 (80.0%)	16 (53.3%)	4.800 [§]	0.029 [*]

The continuous variables are presented as mean \pm standard deviation or median (minimum to maximum). †, ‡, and § represent t, Z, and χ^2 value, respectively; *P < 0.05 represents having statistically significance. AS, ankylosing spondylitis; BASRI-hip, Bath Ankylosing Spondylitis Radiology Hip Index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PSM, propensity score matching; ROM, range of motion; TNF- α , tumor necrosis factor- α .

suppose that the severity of hip involvement could be one of the causes of gender differences in AS. Previous studies have shown that radiographic changes in spine are seen more often^{11,12} and radiographic damage is worse in men with AS^{8,13,14}. To our knowledge, gender differences with respect to advanced hip involvement in AS patients have not been reported.

Gender Differences in Hip Involvement

At present, the effective treatment for AS patients with advanced hip disease is THA, which can greatly improve hip function²³. We found that men underwent THA earlier than women in AS patients, which implies hip involvement in men showing an earlier onset age or faster progress. Similar to recent studies^{5,7,9,15}, we determined that men were younger than women at the onset of hip involvement. Since early onset of disease has been proven to be a risk factor for THA in AS patients³⁰, it is not surprising that men with AS undergo THA earlier than women. The disease duration had no difference between men and women, although it lasted slightly longer in men. Additionally, men had a higher frequency of bilateral onset in hips than women in the AS patients, but no gender difference was found in the frequency of bilateral advanced hip involvement eventually. This inconsistency of hip disease pattern between gender indicates that bilateral onset is the dominant pattern in men, while unilateral onset is more common in women. In terms of the severity of advanced hip involvement, men were more severe than women, with a higher proportion of flexion contracture and ROM = 0° in their hips. Meanwhile, men had a significantly greater spinal involvement rate than women in the patients. Studies on sex differences in CRP levels of AS patients showed significantly higher baseline levels in men compared to women^{5,9,14,15,20}. In our study, although the baseline levels of CRP in men were higher than that in women, the difference did not attain statistical threshold between gender. However, men showed a higher frequency of an elevated level of CRP compared with women in the patients. Based on the above evidence, we conclude that the disease pattern and the severity of hip involvement in AS also has gender differences, particularly in the pattern of onset.

Gender Differences after Adjustment

Given the potential influence of age at onset and disease duration on the severity of hip involvement³⁰, we compared the data again after adjusting for the onset age and disease duration between the two groups by a PSM method. After the adjustment, the male predominance of disease in AS was shown in three aspects, including bilateral onset in hips, spinal involvement, and an elevated level of CRP. Consistent with that before adjustment, the frequency of bilateral advanced hip involvement remained having no gender difference in the patients. The results after adjustment indicate that the gender differences in the onset and outcomes of hip involvement are relatively independent disease processes in AS and are not affected by the onset age and disease duration. Additionally, our study found that

the prevalence of spinal involvement was higher in men than that in women, regardless of PSM being performed between the two groups. Therefore, we consider that the higher prevalence of spinal involvement in men with AS may be responsible for the more severe functional impairment compared with that in women. The same result in gender difference was found in the frequency of an elevated level of CRP after adjustment, which is another consistency. However, data on ESR levels were inconclusive to identify sex differences, regardless of adjustment. Rusman *et al.* suggested that a possible explanation for finding no clear differences in ESR levels could be the already different cut-off levels for normal ESR levels by sex (15 mm/1 h for men vs 20 mm/1 h for women)²¹.

Limitations

The present study has several limitations. First, our study was based on a retrospective analysis. Therefore, some other meaningful clinical characteristics or laboratory values that were not recorded in the medical data could not be investigated. Second, there may be a possible recall bias concerning the onset age in hip involvement and detailed information on drug intervention. Third, this is a single center study which may result in admission bias. A multicenter and multidisciplinary study with a larger observational cohort may be more convincing in future studies.

Conclusions

In summary, we determine that the disease pattern of hip involvement in AS has gender differences. Men develop hip involvement at a younger age and undergo THA earlier than women in AS patients. Bilateral onset is the dominant pattern of hip involvement in men, while unilateral onset is more common in women. However, the frequency of bilateral advanced hip involvement has no gender difference eventually. Besides, men have more severe advanced hip involvement in AS patients compared with women, with a higher proportion of flexion contracture and ROM = 0° in their hips. The prevalence of spinal involvement is higher in men with AS than that in women, which may be responsible for the more severe functional impairment in men.

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Author Contributions

Liang-liang Li designed the study and wrote the article. Jun Fu, Chi Xu, and Ming Ni participated in the analysis of the data and contributed to the interpretation of results. The operations were mainly performed by Wei Chai, Li-bo Hao, Yong-gang Zhou, and Ji-ying Chen, who were the four experienced senior surgeons in our department. All authors read and approved the final manuscript.

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