CLINICAL SCIENCE

Gender differences in ankylosing spondylitis-associated cumulative healthcare utilization: a population-based cohort study

Hsin-Hua Chen, Tzeng-Ji Chen, Yi-Ming Chen, Chiu Ying-Ming, Der-Yuan Chen

1 Taichung Veterans General Hospital - Division of Allergy, Immunology and Rheumatology, Taiwan. 2 National Yang-Ming University - School of Medicine, Taipei, Taiwan. 3 Changhua Christian Hospital - Division of Allergy, Immunology and Rheumatology. 4 Chunghua, Taiwan, Chung-Shan Medical University - School of Medicine Taichung, Taiwan. 5 Chung-Shan Medical University - School of Medicine, Taichung, Taiwan.

BACKGROUND: Ankylosing spondylitis (AS) is one of the most common rheumatic diseases with gender differences in prevalence and clinical presentation. This study aimed to examine whether such gender differences are correlated with cumulative healthcare utilization in Taiwan.

METHODS: The National Health Insurance Research Database supplied claim records of one million individuals from 1996 to 2007. Selected cases included patients aged ≥16 years. Certified rheumatologists diagnosed the patients in three or more visits and gave prescriptions for AS. Multivariate adjusted logistic regression analyses were used to calculate the influence of gender on cumulative healthcare utilization associated with AS.

RESULTS: The study included 228 women and 636 men. After adjustment for potential confounding factors, men had more cumulative outpatient visits associated with AS (odds ratio, 1.59; 95% confidence interval, 1.13 - 2.23; p = 0.008). Men also exhibited a trend for higher frequency of AS-related hospitalization (p = 0.054).

CONCLUSION: Men are more likely to have high cumulative AS-associated healthcare utilization than women. Further investigation of the causal factors is warranted.

KEYWORDS: Administrative database; Ankylosing spondylitis; Gender difference; Health-care utilization; Population-based study.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by pain and stiffness of the back and peripheral joints, with extra-articular manifestations. It often develops in late adolescence but is usually diagnosed in young adults. It is one of the most common rheumatic diseases with gender differences in prevalence and clinical presentation. Although there is male predominance, the ratio of men to women has declined from 9-10:1 in earlier studies to 2:3:1 in recent ones.

Previous studies also show that women have a longer delay in diagnosis, more pain in the cervical spine and peripheral joints, less thoracic and lumbar spinal radiographic severity, lower Bath Ankylosing Spondylitis Radiology Index scores, and more functional limitations at the same level of radiographic damage. However, whether there are gender differences in cumulative healthcare utilization is unknown.

The purpose of this study was to examine the influence of gender on healthcare utilization associated with AS, based on the Taiwanese National Health Insurance Research Database (NHIRD) from 1996 to 2007.

PATIENTS AND METHODS

Data source

The source of data was the NHIRD, covering in-patient and ambulatory care claims in the period 1996-2007. In Taiwan, the compulsory National Health Insurance Program was implemented in March 1995 and covered more than 95% of the population. The Bureau of National Health Insurance (NHI) was the sole buyer of health services and regulated payments for medical care. Its computerized database was a good source for a population-based study.

This study used a representative database extracted randomly from the entire NHIRD dataset in 2005. The database had 1 000 000 persons, or approximately 5% of
Taiwan’s population. Because the NHIRD consisted of deidentified secondary data released to the public for research purposes, this study was exempt from full review by the Internal Review Board. Self-treatment with over-the-counter (OTC) medications or alternative health services were not included in the database.

Although blood tests and radiographic data were not available in the database, the Bureau of NHI audited the accuracy of diagnoses by routinely sampling patient charts randomly to cross-check claims from all hospitals. Any hospital found to have discrepancies, malpractice, or overcharging faced heavy penalties. The audit of the Bureau of NHI promoted the accuracy of coding. 10

Patients
This was a retrospective cohort study. Only those who had claims data in 2006 and 2007 were selected to exclude those who might be dead or lost to follow-up after 2005 (n = 893 859). The AS cases were defined as those with the code 729.0 in the International Classification of Diseases, Ninth Revision (ICD-9) listed for an out-patient visit or hospitalization (i.e. provider-diagnosed AS). Those with three or more AS-associated out-patient visits, with prescription of AS-related drugs (i.e. non-steroid anti-inflammatory drugs [NSAIDs], methotrexate, sulfasalazine, steroids) were selected (n = 1608). To minimize the possibility of misdiagnosis, only those with at least three consensus AS diagnoses by certified rheumatologists were initially included (n = 976). Those aged <16 years in 1996 (n = 112) were also excluded. In the end, 228 women and 636 men with AS were included.

Variables of interest
Gender was the independent variable of interest. Outcome variables included cumulative out-patient visits, frequency of ophthalmic out-patient visit for uveitis, frequency of emergencies, AS-associated in-patient and rehabilitation visits, and frequencies of prescribed AS-related drugs. Healthcare utilization data was dichotomized, i.e. high vs. low, according to the 50th percentile because these were not normally distributed.

Potential confounders included age, duration of follow-up (period between the date of first AS-associated visit and end of 2007), insured amount, and Charlson co-morbidity index (CCI). Insured amount was calculated from the patients’ average monthly income and thus, also served as an economic index. Insured amount were transformed to ordinal variables according to the 25th, 50th and 75th percentile. CCI, adapted by D’Hoore,11 was calculated using diagnostic dose (ICD-9) listed for any out-patient and in-patient visits between the date of the first and the last AS-related visit. CCI was grouped into four ordinal categories: 0, 1, 2, and ≥3.

Statistical analysis
To examine the unadjusted male-female comparisons, t-tests were used for normally distributed continuous variables, Mann-Whitney U tests for continuous variables that were not normally distributed, and χ² tests for categorical variables. Correlations between ordinal variables were studied using the Kendall Tau rank correlation coefficient, while correlations between dichotomous variables were studied using the Phi correlation efficient. Multivariate adjusted logistic regression was used to examine the influence of gender on outcome variables. A two-tailed p < 0.05 was considered statistically significant. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) for Windows Version 13.0 (SPSS, Inc., Chicago, Illinois).

RESULTS
The study cohort included 228 women and 636 men with AS. Their economic-demographic data and co-morbidity were compared in Table 1. Men showed an earlier age onset of healthcare utilization. Further analysis for ordinal variables showed a weak but positive correlation between age and Charlson co-morbidity index (Kendall’s tau rank correlation coefficient = 0.189, p < 0.001).

The cumulative AS-associated healthcare utilization between men and women were compared in Table 2. Men had higher risks of having higher cumulative healthcare visits associated with AS and showed a trend for higher frequency of hospitalization (p = 0.076). Frequencies of AS-related drug use between men and women were not different. There was a significant positive correlation between use of sulfasalazine and use of methotrexate (Phi correlation coefficient = 0.167, p < 0.001).

After adjustment for gender, age, follow-up duration, insured amount, and CCI, men had increased risk of higher cumulative out-patient visits compared to women (odds ratio [OR] 1.59, 95% confidence interval [CI]: 1.13-2.23, p = 0.008) (Table 3). Men also showed a trend for higher frequency of hospitalization (p = 0.054). Other significant predictors of higher healthcare utilization included longer follow-up duration and higher CCI.

Table 1 - Comparison of economic, demographic and co-morbidity between men and women with ankylosing spondylitis patients*. Values are median (inter-quartile range).

| Variable                      | Women (n = 228) | Men (n = 636) | p value |
|-------------------------------|----------------|--------------|---------|
| Age (yrs)                     | 32 (25-41)     | 30 (23-39)   | 0.034   |
| Age group (yrs)               |                |              |         |
| 16-30 (%)                     | 43.0           | 50.5         | 0.204   |
| 31-45 (%)                     | 42.5           | 39.3         |         |
| 46-60 (%)                     | 13.2           | 8.8          |         |
| 61-75 (%)                     | 1.3            | 1.3          |         |
| >75 (%)                       | 0.0            | 0.2          |         |
| Age at utilization onset**    | 38 (30-46)     | 35 (28-44)   | 0.001   |
| (yrs)                         |                |              |         |
| Insured amount                |                |              |         |
| group(NTS)                    |                |              |         |
| < 12800 (%)                   | 32.0           | 21.5         | <0.001  |
| 12800-20000 (%)               | 29.8           | 26.6         | 0.343   |
| 20000-31000 (%)               | 21.5           | 22.8         | 0.712   |
| >31000 (%)                    | 16.7           | 29.1         | <0.001  |
| Charlson co morbidity index   |                |              | <0.001  |
| group                         |                |              |         |
| 0 (%)                         | 45.2           | 60.1         | <0.001  |
| 1 (%)                         | 24.1           | 12.7         | <0.001  |
| 2 (%)                         | 11.8           | 8.6          | 0.187   |
| ≥3 (%)                        | 18.9           | 18.6         | 0.921   |

*Age at utilization onset was defined as the age of initial out-patient or in-patient visit. P values were determined by chi-square tests.
However, in contrast to the current study, theirs
21 outpatient
5-8, 14
Second, the longer
Furthermore, over 98% of Taiwan’s
Moreover, their study has been
Unlike the PSOAS
This

Abbreviation: CCI, Charlson co-morbidity index
Abbreviations: REHA, rehabilitation; OPH, ophthalmic; NSAID, non-

DISCUSSION
The main question addressed by this study is whether or
Not there is gender difference in healthcare utilization
associated with ankylosing spondylitis. By current knowl-
edge, this is the first study to demonstrate that men are
more likely to have higher cumulative AS-associated out-
patient visits compared to women. Singh et al., using a
population based administrative database, report that
gender does not influence healthcare utilization in AS
patients. However, in contrast to the current study, their
investigated both AS and non-AS related healthcare utiliza-
tion for only one year. Moreover, their study has been
limited in examining the gender factor because of male
predominance in the veteran population.
There are several possible explanations to the findings
here. First, men may have worse disease severity that drives
higher healthcare utilization. Worse severity in men has
been reported by Lee et al. However, different from the
current cohort, their cohort is composed of AS patients
with >20 years duration and older age. Second, the longer
delay in diagnosis in women previously reported may be a
cause of later age of utilization onset found in this study and
lead to an underestimation of healthcare utilization.
Another possibility is the existence of gender difference in
the general preference for healthcare utilization. However,
the finding that men have lower healthcare utilization than
women in a recent study from Taiwan provides supportive
evidence to exclude this possibility. The present study reveals a male-to-female ratio of 2.79, consistent with recent reports. Unlike the PSOAS cohort, women in this cohort do not have higher frequencies of sulfasalazine, methotrexate, and intra-articular steroid use. Furthermore, frequencies of sulfasalazine and steroid use in this cohort are higher than those in the PSOAS cohort. These differences may be due to a recall bias in the PSOAS cohort or ethnic differences.
This study has three advantages. First, use of an
administrative database avoids the problem of under-
reporting at higher numbers of visit. Previous studies show that healthcare utilization in AS patients assessed in
administrative databases is higher than that assessed by patient report. Second, a long observation period offers the opportunity to capture the real impact of AS.
Third, this study has adjusted for confounding factors,
including age, gender, follow-up duration, economic status,
and Charlson co-morbidity index (CCI). The CCI, originally
developed to predict mortality from medical records, has
been adapted for administrative databases that use the
International Classification of Diseases, Ninth Revision
(ICD-9). CCI also reportedly influences healthcare utiliza-
tion in osteoarthritis, a chronic rheumatic disease. This
study assumes that CCI may also influence healthcare
utilization in AS and the data proves this. Although other
possible confounding factors, including educational level,
marital status, employment status, race, and current smok-
ing status are unknown, none are significant predictors in
the Singh’s study. Furthermore, over 98% of Taiwan’s
residents are of Chinese Han ethnicity, so the homogenous
population is unlikely to be confounded by race. However,
it also limits the generalization of the study result to other
ethnicities.
This study has several limitations. First, although restric-
tive inclusion criteria have been used, bias due to miscoding
and misclassification can still happen. Second, although this
study uses a 12-year database, underestimation of health-
care utilization in patients with earlier or later disease onset
cannot be discounted. Third, the NHIRD lacks the informa-
tion for self-treatment with OTC medications, which may be

Table 2 - Comparison of cumulative healthcare utilization associated with ankylosing spondylitis between men and women (1996-2007)*.

| Model characteristics | Women (n = 228) | Men (n = 636) | p value |
|-----------------------|----------------|--------------|---------|
| Follow-up duration (yrs) | 5.8 (3.1-8.0) | 7.1 (4.7-8.7) | <0.001 |
| Number of outpatient visits | 15.0 (9.0-31.8) | 22.0 (12.0-47.0) | <0.001 |
| ≥ 21 outpatient visits (%) | 39.0 | 53.9 | <0.001 |
| ≥ 1 hospitalization (%) | 7.0 | 10.5 | 0.076 |
| ≥ 1 emergent visit (%) | 6.6 | 5.5 | 0.620 |
| ≥ 1 REHA visit (%) | 16.7 | 20.9 | 0.176 |
| ≥ 1 OPH visit for uveitis (%) | 18.4 | 17.3 | 0.686 |
| NSAID use (%) | 100 | 99.8 | 1.000 |
| Methotrexate use (%) | 21.5 | 16.7 | 0.108 |
| Sulfasalazine use (%) | 81.6 | 86.9 | 0.062 |
| Oral steroid use (%) | 86.8 | 83.6 | 0.287 |
| Intra-articular steroid use (%) | 2.6 | 2.8 | 1.000 |

*Values are median (inter-quartile range)
Abbreviations: REHA, rehabilitation; OPH, ophthalmic; NSAID, non-steroidal anti-inflammatory drugs

Table 3 - Significant predictors of utilization associated with ankylosing spondylitis, by multivariate analyses*.

| Model characteristics | Significant predictors | OR (95% CI) | P-value |
|-----------------------|-----------------------|-------------|---------|
| Hosmer-Lemeshow test   | 11.326 (p = 0.184)    | 5.362 (p = 0.068) |
| Nagelkerke R²           | 0.173                 | 0.250       |
| -2 log likelihood       | 1077.399              | 439.114     |

| Model characteristics | Hospitalization (yes) | OR (95% CI) | P-value |
|-----------------------|-----------------------|-------------|---------|
| Male gender           | 1.59 (1.13-2.23)      | 1.83 (0.99-3.41) | 0.054 |
| Follow-up duration    | 1.26 (1.19-1.34)      | 1.24 (1.10-1.39) | <0.001 |
| CCI                   | <0.001                | <0.001       |
| 1                     | 1.64 (1.08-2.48)      | 11.34 (5.11-25.13) | <0.001 |
| 2                     | 1.42 (0.86-2.34)      | 6.86 (2.71-17.38) | <0.001 |
| ≥3                    | 2.43 (1.60-3.67)      | 15.67 (7.43-33.07) | <0.001 |

*Multivariable regression models adjusted for the following variables: gender, age, follow-up duration, Charlson co-morbidity index, and insured amount.
Abbreviation: CCI, Charlson co-morbidity index
a confounding factor. However, a recent study from Taiwan does not reveal gender in preference for OTC medication use. Lastly, other possible confounding factors like the duration of leaving, retirement status, and disease duration are unavailable in the NHIRD. However, if a Taiwanese resident migrates to other countries, the Bureau of NHI will abrogate his/her insurance.

This study excludes those without claims data in 2006 and 2007, which ensured that the enrolled patients did not have long-term leaving. As for short-term leaving, because the Bureau of NHI allows patients’ families to visit doctors and take medicines for the patients, the influence of short-term leaving on the number of out-patient visits may be reduced. Because the insured amount is determined by average monthly income, the adjustment for insured amount in this study may also comprise adjustments for the status of retirement.

The true disease duration of AS is difficult to obtain via claims data because the duration between age at symptom onset and age at diagnosis usually lasts for several years and varies widely. Ward’s study also shows that cumulative five-year total costs of AS, which may be related to cumulative out-patient and in-patient visits, are not influenced by disease duration. In conclusion, this study demonstrates that men are more likely to have higher cumulated AS-associated out-patients visits compared to women. Further studies are required to examine whether higher AS-related cumulative healthcare utilization in men is caused by worse disease severity and/or shorter delay in diagnosis.

REFERENCES
1. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002;61 Suppl 3:iii8-18.
2. Lee W, Reveille JD, Weisman MH. Women with ankylosing spondylitis: a review. Arthritis Rheum 2008;59:449-54, doi: 10.1002/art.23321.
3. Polley HF SC. Rheumatoid spondylitis: a study of 1,035 cases. Ann Intern Med 1947;26:240-9.
4. West HF. Aetiology of Ankylosing Spondylitis. Ann Rheum Dis 1949;8:143-8, doi: 10.1136/ard.8.2.143.
5. Masi AT, Wilkins WR. Does malefemale sex ratio in ankylosing spondylitis change with age? J Rheumatol 1996;23:947-8.
6. Will R, Edmunds L, Elswod J, Calin A. Is there sexual inequality in ankylosing spondylitis? A study of 498 women and 1202 men. J Rheumatol 1990;17:1649-52.
7. Lee W, Reveille JD, Davis JC Jr., Learch TJ, Ward MM, Weisman MH. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. Ann Rheum Dis 2007;66:633-8, doi: 10.1136/ard.2006.060293.
8. Boonen A, van der Heijde D, Landewe R, Guillemijn F, Spoorenberg A, Schouten H, et al. Costs of ankylosing spondylitis in three European countries: the patient’s perspective. Ann Rheum Dis 2003;62:741-7, doi: 10.1136/ard.62.8.741.
9. Bureau of National Health Insurance. National Health Insurance Annual Statistical Report. Bureau of National Health Insurance, Taipei; 20th.
10. Chen TM. Taiwan’s new national health insurance program: genesis and experience so far. Health Aff 2003;22:61-76, doi: 10.1377/hlthaff.22.3.61.
11. DeHooe W, Bouchaer A, Tilquin C. Practical considerations on the use of the Charlson co-morbidity index with administrative data bases. J Clin Epidemiol 1996;49:1429-33, doi: 10.1016/S0895-4356(96)00271-5.
12. Singh JA, Strand V. Health care utilization in patients with spondyloarthropathies. Rheumatology 2009;48:272-6, doi: 10.1093/rheumatology/ker472.
13. Lin TF. Modifiable health risk factors and medical expenditures - The case of Taiwan. Soc Sci Med 2008;67:1727-36, doi: 10.1016/j.socscimed.2008.09.010.
14. Verstappen SM, Jacobs JW, van der Heijde DM, van der Linden S, Verhoeff CM, Bijloma JW, et al. Utility and direct costs: ankylosing spondylitis compared with rheumatoid arthritis. Ann Rheum Dis 2007;66:727-31, doi: 10.1136/ard.2006.061283.
15. Roberts RO, Bergstrahl Ej, Schmidt L, Jacobsen SJ. Comparison of self-reported and medical record health care utilization measures. J Clin Epidemiol 1996;49:989-95, doi: 10.1016/0895-4356(96)00143-6.
16. Kobelt G, Andlin-Sobocki P, Maksymowycz WP. Costs and quality of life of patients with ankylosing spondylitis in Canada. J Rheumatol 2006;33:289-95.
17. Zink A, Thiele K, Huscher D, Listing J, Sieper J, Krause A, et al. Healthcare and burden of disease in psoriatic arthritis. A comparison with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol 2006;33:86-90.
18. Boonen A, van der Heijde D, Landewe R, Guillemijn F, Rutten-van Molken M, Dougados M, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. Ann Rheum Dis 2003;62:732-40, doi: 10.1136/ard.62.8.732.
19. Boonen A, van den Heuvel R, van Tubergen A, Goossens M, Severens JL, van der Heijde D, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. Ann Rheum Dis 2005;64:396-402, doi: 10.1136/ard.2003.019711.
20. Charlson ME, Pompei P, Ales KL, McKinzie CR. A new method of classifying prognostic co-morbidity in longitudinal studies: Development and validation. J Chron Dis 1987;40:373-83, doi: 10.1016/0021-9681(87)90171-8.
21. Dominick KL, Dudley TK, Coffman CJ, Bosworth HB. Comparison of three co-morbidity measures for predicting health service use in patients with osteoarthritis. Arthritis Rheum 2005;53:666-72, doi: 10.1002/art.21440.
22. Liu CY, Liu JS. Socioeconomic and demographic factors associated with health care choices in Taiwan. Asia Pac J Public Health 2010;22:51-62.
23. Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. Arthritis Rheum 2002;46:223-31, doi: 10.1002/art.10479.