의학석사 학위논문

Incidence of end-stage renal disease in ankylosing spondylitis:

a nationwide population-based study

강직성 척추염에서 말기 신부전의 발생률:

국민 건강 보험 공단 자료를 기반으로 한 연구

2021 년 2 월

서울대학교 대학원

의과대학 내과학

조 세 민

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이 논문을 의학석사 학위논문으로 제출함

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조 세 민의 석사 학위논문을 인준함

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Abstract

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Background: This study aimed to evaluate end-stage renal disease (ESRD) incidence after the diagnosis of ankylosing spondylitis (AS) and the clinical significance of incident ESRD in patients with AS.

Methods: Using the Nationwide Health Insurance Database of South Korea, subjects diagnosed with AS between 2009 and 2016 were included. The AS group was matched with a control group considering age, sex, and inclusion year. The incidence of ESRD in the AS group was compared with the control group. In addition, the relationship between the incident ESRD and all-cause mortality was analyzed in the AS group.

Results: A total of 7,563 patients with AS were enrolled in this study.

The patients with AS showed a higher incidence of ESRD than the control group after the adjustment of age, sex, body mass index, smoking history, income level, and comorbidities (hazard ratio [HR], 4.11; 95% confidence interval [CI], 1.60–10.57; *p*–value, 0.003). Only age was identified as a risk factor for predicting the development of ESRD. In the AS group, the occurrence of ESRD was found to increase mortality statistically significantly.

Conclusion: Patients with AS showed a higher risk of ESRD than matched control groups even after adjusting comorbidities. Furthermore, it was confirmed in AS group that the development of ESRD increases all–cause mortality.

Keywords: end–stage renal disease, ankylosing spondylitis, national health insurance data

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국문 초록

배경: 본 연구는 강직성 척추염으로 진단받은 이후 말기 신부전의 발생률을 확인하고, 말기 신부전의 발생이 가지는 임상적 중요성을 보고자 한다.

방법: 대한민국의 국민건강보험공단 자료를 활용하여 2009년부터 2016년까지 강직성 척추염으로 진단된 환자들을 추출하였다. 강직성 척추염으로 진단된 환자들의 나이, 성별, 연구에 포함된 년도를 고려하여 대조군을 설정하였다. 이후 통계 분석을 통해 강직성 척추염으로 진단된 이후의 말기 신부전 발생률을 대조군과 비교하였다. 또한 강직성 척추염 환자에서의 말기신부전 발생과 사망률과의 관계를 분석하였다.

연구결과: 강직성 척추염군에 총 7,563명이 포함되어 분석되었다. 분석결과 나이, 성별, 체질량지수, 흡연력, 경제수준, 동반질환을 보정함에도 불구하고 강직성 척추염군에서 대조군에 비해 말기신부전의 발생률이 높았다. (위험비, 4.11; 95% 신뢰구간, 1.60−10.57; p−value, 0.003) 위험인자로는 고령일수록 말기 신부전의 발생이 높았다. 강직성 척추염군에서는 말기 신부전의 발생이 통계적으로 유의하게 사망률의 증가와 관련이 있었다.

결론: 강직성 척추염으로 진단된 환자들이 동반 질환을 보정한 후에도 대조군에 비해 말기 신부전의 발생 위험이 높았다. 또한 강직성 척추염군에서 말기 신부전의 발생은 사망률이 높아짐과 연관됨을 확인하였다.

키워드: 말기 신부전, 강직성 척추염, 국민 건강 보험 자료

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Introduction

End-stage renal disease (ESRD) is a condition in which the estimated glomerular filtration rate (eGFR) has decreased to less than 15 mL/min/1.73m^2. Eventually, it needs renal replacement therapy such as hemodialysis, peritoneal dialysis, or kidney transplantation. In Korea, the average yearly increase in the incidence of treated ESRD patients was 19.4 per million population between 2009-2010 and 2017-2018.[1] ESRD is one of the independent risk factors that increase mortality, and the known causes of death include cardiovascular disease and infection, etc.[2] The cost for dialysis in ESRD patients was estimated to be 1.5 billion USD in 2013, which constitutes a considerable portion of the overall national health insurance budget compared to the prevalence of ESRD.[3] Therefore, considering both the medical and social aspects, it is crucial to assess the risk of ESRD and predict the likelihood.

Ankylosing spondylitis (AS) is a chronic inflammatory disease mainly involving the axial skeleton and sacroiliac joint.[4] The epidemiologic study of AS in South Korea showed that the prevalence

increased linearly by 7.7% annually.[5] Common extra-articular manifestations are uveitis, psoriasis, and inflammatory bowel disease. While the kidney involvement of AS might not be frequent[6], it is known to show pathological diagnosis such as renal amyloidosis, non-steroidal anti-inflammatory drugs (NSAIDs) nephropathy, IgA nephropathy.[6-8] The extraarticular manifestation including kidney could be a consequence of uncontrolled systemic inflammation.[9] As a feature of AS, chronic systemic inflammation affects the entire body, such as coronary heart disease, metabolic syndrome, diabetes mellitus, and aging, through reactive oxygen species and several inflammatory cytokines.[10-13]

This study was aimed to evaluate the risk of progression to ESRD after diagnosis of AS using national health insurance data.

Methods

2.1 Ethical consideration

This study complied the Declaration of Helsinki. The institutional review board of Seoul National University Hospital (institutional review board no. E-1906-002-1035) approved the study. The attending government organization approved the usage of the National Health Insurance Service (no. NHIS-2020-1-047).

2.2 Study population

Nationwide population-based data from the National Health Insurance Database of South Korea from January 2009 to December 2016 were reviewed. Patients newly diagnosed with AS were selected from 2009 to 2016 through the specific diagnostic code for the registration system of the rare incurable disease. The exclusion criteria were as follows: 1) age less than 19 years, 2) previously diagnosed with ESRD, 3) previously treated with hemodialysis, peritoneal dialysis, and kidney transplantation.

The control group without the diagnosis of AS and history of renal replacement therapy before was matched 1:1 with the AS group considering age, sex, and inclusion year through age–sex stratification matching.

2.3 Data collection

Data from the National Health Insurance Database was reviewed and collected. Demographic characteristics included age, sex, body mass index (BMI), smoking history, and income level. Medical history of hypertension, diabetes mellitus, congestive heart failure, and cancer was collected as comorbidities. The medications, including NSAIDs, steroids, disease–modifying anti–rheumatic drugs (DMARDs), and tumor necrosis factor–α (TNF–α) inhibitors, were investigated in the AS group analysis.

2.4 Study outcomes

The primary outcome was to identify the incidence of ESRD after

diagnosis of AS. Incident ESRD was defined as a case in which a specific code for hemodialysis or peritoneal dialysis was issued for more than 90 days and kidney transplantation after the diagnosis of AS. The analysis for predictive risk factor for progression to ESRD in the AS group was conducted. The secondary outcome was the effect of incident ESRD on the prognosis of AS patients as all-cause mortality.

2.5 Statistical analysis

The continuous variables were presented as mean ± standard deviation and categorical variables as a percentage. The student *t*-test and chi-squared test were used to investigate the difference between the AS and the control group. Incidence of ESRD in those two groups were expressed by the number of events by 1,000 person-years. The cumulative incidences of ESRD were examined by the Kaplan-Meier method and the log-rank test. Cox proportional hazard regression models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of incident ESRD in AS

patients. The SAS 9.4 program (SAS Institute) was used to perform the statistical analysis. A p−value <0.05 was considered statistically significant.

Results

3.1 Baseline characteristics

A total of 7,563 patients with AS and age, sex, and inclusion year–matched control group were enrolled in the study (Figure 1). Baseline characteristics, including demographic data, comorbidities, and medications are shown in Table 1. There was no difference in age and sex ratio and no statistically significant difference in smoking history and prevalence of hypertension in the AS and control group. The AS group was lighter, lower economic status, and had a higher prevalence of congestive heart failure and cancer than the control group. In addition, the rate of using all medications (NSAIDs, steroids, DMARDs, and TNF–α inhibitors) was statistically significantly higher in the AS group than the control group.

3.2 Incidence and risk factors of ESRD

The incidence of ESRD was higher in the AS group than in the control group. The HR of incident ESRD in the AS group was 3.90

(95% CI, 1.49–8.02; p–value, 0.004) after adjustment for age, sex, BMI, smoking history, income level, and presence of hypertension, diabetes mellitus, congestive heart failure and cancer. After additional adjustment for medications including NSAIDs, DMARDs, steroids and TNF–α inhibitors, the HR of incident ESRD in the AS group was still higher than in the control group (HR, 4.11; 95% CI, 1.60–10.57; p–value, 0.003) (Table 2). Higher incidence probability of ESRD in the AS group than the control group was shown in Figure 2.

Among the clinical characteristics, only age is an independent risk factor for incident ESRD in AS patients (HR, 1.07; 95% CI, 1.03–1.11; p–value <0.001). The comorbidities such as hypertension and diabetes mellitus and history of NSAIDs were not related to increase the incident ESRD in the AS group (Table 3).

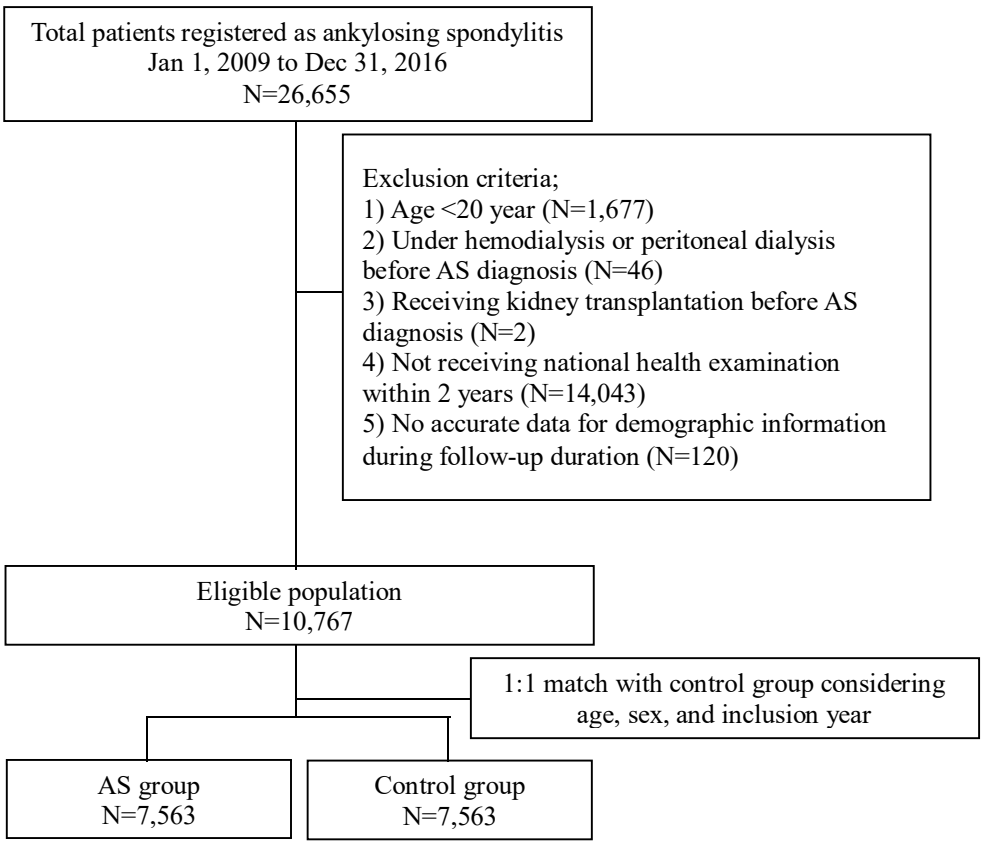

Figure 1. Flow chart

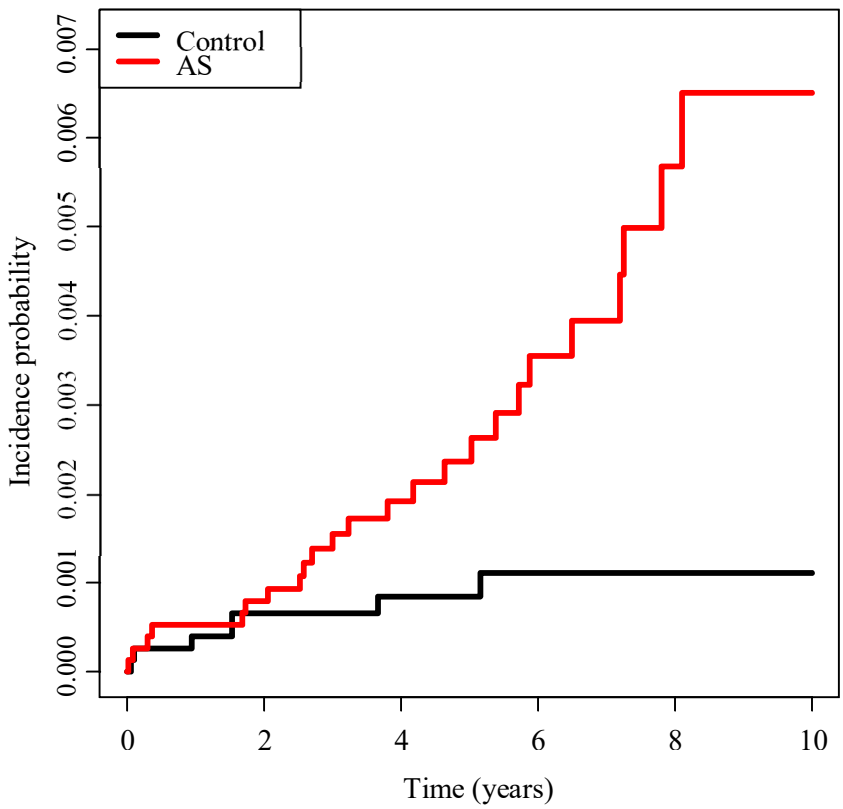

Figure 2. Incidence probability of ESRD in the AS group and the control group

Table 1. Baseline characteristics of the AS group and the control group

	AS (N=7,563)	Control (N=7,563)	p-value
Age (years) (%)			1
20-29	548 (7.25)	548 (7.25)	
30-39	1,785 (23.60)	1,785 (23.60)	
40-49	2,004 (26.50)	2,004 (26.50)	
50-59	1,733 (22.91)	1,733 (22.91)	
60-69	1,003 (13.26)	1,003 (13.26)	
≥70	490 (6.48)	490 (6.48)	
Male (%)	5,394 (71.32)	5,394 (71.32)	1
BMI (%)			0.007
Underweight*	186 (2.46)	127 (1.68)	
Normal weight*	4,627 (61.18)	4,629 (61.21)	
Overweight*	2,391 (31.61)	2,458 (32.50)	
Obesity*	359 (4.75)	349 (4.61)	
Smoking history (%)			0.042
Never smoker	3,631 (48.01)	3,641 (48.14)	
Ex-smoker	1,561 (20.64)	1,449 (19.16)	
Current smoker	2,371 (31.35)	2,473 (32.70)	
Income level (%)			<0.001
1st quartile	1,523 (20.14)	1,392 (18.41)	
2nd quartile	1,306 (17.27)	1,456 (19.25)	
3rd quartile	2,043 (27.01)	2,182 (28.85)	
4th quartile	2,691 (35.58)	2,533 (33.49)	
Comorbidities (%)			
Hypertension	992 (13.12)	1,070 (14.15)	0.065
Diabetes mellitus	399 (5.287)	519 (6.86)	<0.001
Congestive heart failure	36 (0.48)	20 (0.26)	0.032
Cancer	216 (2.86)	157 (2.08)	0.002
Medications (%)			
NSAIDs	6,202 (82.00)	4,349 (57.50)	<0.001
Steroids	2,705 (35.77)	1,172 (15.50)	<0.001
DMARDs	3,984 (52.68)	33 (0.44)	<0.001
TNF-α inhibitors	79 (1.04)	0 (0)	<0.001

Abbreviation: AS, ankylosing spondylitis; BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs

*Underweight: BMI <18 kg/m^2, normal weight: 18≤BMI<25 kg/m^2, overweight: 25≤BMI<30 kg/m^2, obesity: ≥30 kg/m^2

Table 2. Incidence rate and risk of ESRD in the AS group compared with the control group

	Total No.	ESRD	IR*	Univariate		Model 1**		Model 2***	
				HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Control	7,563	7	0.17	1 (reference)		1 (reference)		1 (reference)	
AS	7,563	24	0.59	3.46 (1.49-8.02)	0.004	3.90 (1.67-9.09)	0.002	4.11 (1.60-10.57)	0.003

*IR: incidence rate per 1000 person-years

**Model 1 was adjusted for age, sex, BMI, smoking history, income level, and presence of hypertension, DM, congestive heart failure and cancer.

***Model 2 was adjusted for age, sex, BMI, smoking history, income level, presence of hypertension, DM, congestive heart failure, cancer and medications (NSAIDs, DMARDs, steroids, and TNF-α inhibitors).

Table 3. Risk factors for incident ESRD in the AS group

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.08 (1.04-1.11)	<0.001	1.07 (1.03-1.11)	<0.001
Male	0.42 (0.19-0.94)	0.036	0.35 (0.12-1.07)	0.066
BMI		0.999		0.980
Underweight*	0 (0)		0 (0)	
Normal weight*	1 (reference)		1 (reference)	
Overweight*	1.05 (0.44-2.47)		0.86 (0.36-2.06)	
Obesity*	0.93 (0.12-7.05)		0.71 (0.09-5.54)	
Smoking history (%)		0.801		0.308
Never smoker	1 (reference)		1 (reference)	
Ex-smoker	0.73 (0.24-2.25)		1.46 (0.37-5.71)	
Current smoker	0.78 (0.31-1.96)		2.47 (0.76-8.01)	
Income level (%)		0.667		0.968
1st quartile	1 (reference)		1 (reference)	
2nd quartile	0.52 (0.13-2.08)		0.78 (0.19-3.14)	
3rd quartile	0.55 (0.17-1.81)		0.85 (0.26-2.84)	
4th quartile	0.87 (0.32-2.40)		1.03 (0.37-2.89)	
Comorbidities (%)				
Hypertension	3.46 (1.48-8.09)	0.004	2.29 (0.95-5.53)	0.066
Diabetes mellitus	2.86 (0.85-9.59)	0.089	2.21 (0.65-7.59)	0.206
Congestive heart failure	0 (0)	0.991	0 (0)	0.998
Cancer	1.79 (0.24-13.25)	0.570	1.20 (0.16-9.04)	0.862
Medications (%)				
NSAIDs	0.58 (0.24-1.40)	0.223	0.49 (0.20-1.19)	0.114
Steroid	1.36 (0.59-3.13)	0.466	1.11 (0.47-2.59)	0.817
DMARDs	0.72 (0.32-1.60)	0.419	0.96 (0.42-2.20)	0.930
TNF-α inhibitors	0 (0)	0.990	0 (0)	0.995

3.3 Effect of incident ESRD on all-cause mortality

Table 4 shows the effect of incident ESRD on all-cause mortality. The AS patients with ESRD had a higher mortality rate than those without ESRD even after adjusting age, sex, BMI, smoking history, income level, and presence of hypertension, diabetes mellitus, congestive heart failure and cancer (HR, 4.95; 95% CI, 1.96-12.54; *p*-value, 0.001).

Table 4. Risk of all-cause mortality in the AS group with or without ESRD

	Model 1*		Model 2**	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
AS without ESRD	1 (reference)		1 (reference)	
AS with ESRD	13.36 (5.45-32.76)	<0.001	4.95 (1.96-12.54)	0.001

*Model 1 was non-adjusted.

**Model 2 was adjusted for age, sex, BMI, smoking history, income level, and presence of hypertension, diabetes mellitus, congestive heart failure and cancer.

Discussion

This nationwide retrospective cohort study was conducted to investigate the incidence of ESRD in AS patients. This study is the first analysis that the evaluation of incident ESRD after diagnosis of AS in South Korea. Since 2006 in Korea, National Health Insurance started the registration system for rare incurable diseases and provided medial expenses reduction benefits to the patients. As AS belongs to the rare incurable diseases system, the precise prevalence could be determined.

Chronic systemic inflammation affects the vital organs and the pathogenesis of various diseases including chronic kidney disease (CKD) through severel mechanisms. Monocytes and endothelial cells that primarily secret inflammatory cytokines play an important role in systemic inflammation. Considering the ubiquitous distribution of endothelial cell and kidney blood flow, kidney is one of the organs vulnerable to systemic inflammation.[14] Various inflammatory cytokines are known to cause progressive glomerular injury.[15-18] Inflammatory cytokines such as TNF-α, TNF-β, interleukin-1 (IL-

1), IL-6 are known to cause mesangial cell growth,[19, 20] extracellular matrix production,[21] procoagulant activity of endothelium,[22] production of reactive oxygen species[23] and expression of adhesion receptors,[24] bioactive lipids,[25] and metalloproteinase.[26,28] Various blood biomarkers suggesting inflammation have revealed that the degree of systemic inflammation is related to the progression of CKD.[27-29] Several studies have been conducted the renal failure in various diseases characterized by chronic inflammation. One study found that the risk of ESRD was elevated in patients with Crohn's disease (adjusted HR, 6.33; 95% CI, 2.75-14.56) not in patients with ulcerative colitis, so they recommend to monitor carefully for renal insufficiency in patients with Crohn's disease.[5] A meta-analysis to investigate the risk of CKD and ESRD in patients with psoriasis showed that patients with psoriasis had a higher risk of incident CKD (risk ratio [RR], 1.34; 95% CI, 1.14-1.57) and ESRD (RR, 1.29; 95% CI, 1.05-1.60).[30] Celiac disease is an immune-mediated disease with a prevalence of about 1% worldwide.[31] One prospective cohort study showed that the patients with biopsy-proven celiac disease suffer an increased risk of subsequent ESRD (adjusted HR, 2.98; 95% CI, 2.22-3.71).[32]

There were several researches to evaluate the renal complication in AS. A cross-sectional study showed that renal impairment in AS patients was associated with age, HLA-B27 negativity, and elevated acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate.[15] They hypothesized that chronic inflammation could cause renal impairment through atherosclerosis. However, one nationwide retrospective cohort study was conducted in Taiwan using national health insurance database and showed that the risk of incident ESRD in AS patients.[1] They defined treated AS group as having at least three ambulatory visits with an AS diagnostic code and concurrent prescription of NSAIDs, sulfasalazine, methotrexate, and steroids. Compared with the non-AS group 1:10 matched with the treated AS group for age, sex and index date, the incidence of ESRD in the treated AS group was statistically significantly lower than the non-AS group (incidence rate ratio, 0.39; 95% CI, 0.29-0.51). After additional adjustement for NSAIDs, there was no significantly difference in incident ESRD between the treated AS group and non-AS group.

Unlike previous study, the results of this study showed that incident

ESRD was more commonly found in the AS group than the control group even after adjusting age, sex, BMI, smoking history, income level, comorbidities, and medications. Multivariate logistic regression was conducted to figure out the predictive risk factor of progression to ESRD, and only the age was related to increase the risk of ESRD. Furthermore, incident ESRD was related to increase all-cause mortality in AS patients. Regarding the pathophysiology of AS, chronic inflammation could affect the patient's kidney function through damage to cells composing kidney, fibrosis, ROS production, and dysregulation of vascular structure by several inflammatory cell and cytokines.

There were several limitations in this study. This study is the retrospective cohort study. But, based on nationwide insurance database, the number of subjects is relatively large compared with previous studies. Second, despite using national insurance data, the number of outcomes was absolutely small, so that it was difficult to prove the statistical significance at the analysis of risk factor of incident ESRD. Third, this study did not use the result of blood test such as serum creatinine and urine test, because we used data only

from specific diagnostic code registration for rare incurable disease and drug claims data. If only the patient with available blood or urine test results were included, the number of study subjects would have decreased and also the statistical power would have been difficult to obtain. Fourth, the result of the control group in this study may seem underestimated. According to the report of the Korean Society of Nephrology in 2015, there were 12,865 newly diagnosed ESRD patients in South Korea (250 per million population).[33] This can be explained as a selection bias for the age group and sex ratio, considering the 1:1 matching that considered age and sex with the AS group.

Despite some limitations, this study aimed to identify the incidence of ESRD after diagnosis of AS, and relationship between incident ESRD and mortality. The results supported that the renal impairment is dominant in AS patients compared with general population, so I suggest that the evalution of kidney function in AS patients is important. Further studies with serological, pathological, and molecular approach will help to understand the causal relationship between AS and renal impairment.

Reference

1 Chen HH, Lin CH, Lai KL, Hsieh TY, Chen YM, Tseng CW*, et al.* Relative risk of end-stage renal disease requiring dialysis in treated ankylosing spondylitis patients compared with individuals without ankylosing spondylitis: A nationwide, population-based, matched-cohort study. *PLoS One*. 2020; **15**: e0231458.

2 Jin DC, Yun SR, Lee SW, Han SW, Kim W, Park J*, et al.* Lessons from 30 years' data of Korean end-stage renal disease registry, 1985-2015. *Kidney Res Clin Pract*. 2015; **34**: 132-9.

3 Kang YU, Bae EH, Ma SK, Kim SW. Determinants and burden of chronic kidney disease in a high-risk population in Korea: results from a cross-sectional study. *Korean J Intern Med*. 2016; **31**: 920-9.

4 Sieper J, Poddubnyy D. Axial spondyloarthritis. *The Lancet*. 2017; **390**: 73-84.

5 Park JS, Hong JY, Park YS, Han K, Suh SW. Trends in the prevalence and incidence of ankylosing spondylitis in South Korea, 2010-2015 and estimated differences according to income status. *Sci Rep*. 2018; **8**: 7694.

6 Lee SH, Lee EJ, Chung SW, Song R, Moon JY, Lee SH*, et al.* Renal involvement in ankylosing spondylitis: prevalence, pathology, response to TNF-a blocker. *Rheumatol Int*. 2013; **33**: 1689-92.

7 Samia B, Hazgui F, Abdelghani KB, Hamida FB, Goucha R, Hedri H*, et al.* [Renal abnormalities in ankylosing spondylitis]. *Nephrol Ther*. 2012; **8**: 220-5.

8 Gratacos J, Orellana C, Sanmarti R, Sole M, Collado A, Gomez-Casanovas E*, et al.* Secondary amyloidosis in ankylosing spondylitis. A systematic survey of 137 patients using abdominal fat aspiration. *J Rheumatol*. 1997; **24**: 912-5.

9 Elewaut D, Matucci-Cerinic M. Treatment of ankylosing spondylitis and extra-articular manifestations in everyday rheumatology practice. *Rheumatology (Oxford)*. 2009; **48**: 1029-35.

10 Libby P. Inflammation in atherosclerosis. *Nature*. 2002; **420**: 868-74.

11 Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum*. 2005; **52**: 722-32.

12 Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. *Interdiscip Top Gerontol*. 2015; **40**: 99-106.

13 Pawelec G, Goldeck D, Derhovanessian E. Inflammation, ageing and chronic disease. *Curr Opin Immunol*. 2014; **29**: 23-8.
14 Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, *et al.* Inflammation-Related Mechanisms in Chronic Kidney Disease Prediction, Progression, and Outcome. *J Immunol Res*. 2018; **2018**: 2180373.
15 Couderc M, Pereira B, Molto A, Tiple A, Soubrier M, Dougados M. The Prevalence of Renal Impairment in Patients with Spondyloarthritis: Results from the International ASAS-COMOSPA Study. *J Rheumatol*. 2018; **45**: 795-801.
16 Boswell JM, Yui MA, Burt DW, Kelley VE. Increased tumor necrosis factor and IL-1 beta gene expression in the kidneys of mice with lupus nephritis. *J Immunol*. 1988; **141**: 3050-4.
17 el Nahas AM. Growth factors and glomerular sclerosis. *Kidney Int Suppl*. 1992; **36**: S15-20.
18 Ketteler M, Noble NA, Border WA. Transforming growth factor-beta and angiotensin II: the missing link from glomerular hyperfiltration to glomerulosclerosis? *Annu Rev Physiol*. 1995; **57**: 279-95.
19 Coleman DL, Ruef C. Interleukin-6: an autocrine regulator of mesangial cell growth. *Kidney Int*. 1992; **41**: 604-6.
20 Horii Y, Muraguchi A, Iwano M, Matsuda T, Hirayama T, Yamada H, *et al.* Involvement of IL-6 in mesangial proliferative glomerulonephritis. *J Immunol*. 1989; **143**: 3949-55.
21 Nakamura T, Miller D, Ruoslahti E, Border WA. Production of extracellular matrix by glomerular epithelial cells is regulated by transforming growth factor-beta 1. *Kidney Int*. 1992; **41**: 1213-21.
22 Bevilacqua MP, Pober JS, Majeau GR, Fiers W, Cotran RS, Gimbrone MA, Jr. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci U S A*. 1986; **83**: 4533-7.
23 Sharma K, Cook A, Smith M, Valancius C, Inscho EW. TGF-beta impairs renal autoregulation via generation of ROS. *Am J Physiol Renal Physiol*. 2005; **288**: F1069-77.
24 Park S, Chang YH, Cho YJ, Ahn H, Yang WS, Park JS, *et al.* Cytokine-regulated expression of vascular cell adhesion molecule-1 in human glomerular endothelial cells. *Transplant Proc*. 1998; **30**: 2395-7.
25 Zager RA, Johnson A. Renal cortical cholesterol accumulation is an integral component of the systemic stress response. *Kidney Int*. 2001; **60**: 2299-310.
26 Atkins RC. Interleukin-1 in crescentic glomerulonephritis. *Kidney Int*. 1995; **48**: 576-86.
27 Shankar A, Sun L, Klein BE, Lee KE, Muntner P, Nieto FJ, *et al.* Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. *Kidney Int*. 2011; **80**:

1231-8.
28 Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, *et al.* Inflammation and Progression of CKD: The CRIC Study. *Clin J Am Soc Nephrol*. 2016; **11**: 1546-56.
29 Oh YJ, An JN, Kim CT, Yang SH, Lee H, Kim DK, *et al.* Circulating Tumor Necrosis Factor alpha Receptors Predict the Outcomes of Human IgA Nephropathy: A Prospective Cohort Study. *PLoS One*. 2015; **10**: e0132826.
30 Ungprasert P, Raksasuk S. Psoriasis and risk of incident chronic kidney disease and end-stage renal disease: a systematic review and meta-analysis. *Int Urol Nephrol*. 2018; **50**: 1277-83.
31 Rubio-Tapia A, Murray JA. Celiac disease. *Curr Opin Gastroenterol*. 2010; **26**: 116-22.
32 Welander A, Prutz KG, Fored M, Ludvigsson JF. Increased risk of end-stage renal disease in individuals with coeliac disease. *Gut*. 2012; **61**: 64-8.
33 Jin DC, Yun SR, Lee SW, Han SW, Kim W, Park J. Current characteristics of dialysis therapy in Korea: 2015 registry data focusing on elderly patients. *Kidney Res Clin Pract*. 2016; **35**: 204-11.