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Incidence and Prevalence of Juvenile Systemic Lupus Erythematosus in Korea: Data From the 2017 National Health Claims Database

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ABSTRACT. ***Objective.*** The purpose of the present study was to investigate the prevalence and incidence of juvenile systemic lupus erythematosus (JSLE) in Korea.

Methods. The data were collected from the National Health Insurance Claims Database of Korea. JSLE was identified using the diagnostic code M32 from the Korean Standard Classification of Diseases. Patients between 5 and 18 years old, who had at least 1 claim for JSLE from January 1, 2016, to December 31, 2017, as final diagnosis, were analyzed in the study. For prevalent cases, patients who used, at least 1 time, any type of medical services with a diagnostic code of M32 were selected. For incident cases, patients who did not use medical services with the M32 code 1 year prior and who were newly registered in 2017 were defined. Change-point analysis was used to find the age at which changes in prevalence and incidence occurred.

Results. The prevalence of JSLE was 6.92 per 100,000 persons and the incidence of JSLE was 2.76 per 100,000 person-years in patients between 5 and 18 years old. The prevalence and incidence of JSLE were higher in females than in males. According to the change-point analysis, we found that the incidence and prevalence of female patients increased rapidly at the ages of 14 and 15 years, respectively.

Conclusion. This Korean population-based epidemiological study of JSLE showed similar epidemiologic profiles to Asian population in other studies. The distribution of age, ethnicity, and pubertal status are important factors that influence population estimates of JSLE incidence and prevalence.

Key Indexing Terms: change-point, incidence, juvenile systemic lupus erythematosus, Korea, prevalence, systemic lupus erythematosus

The epidemiology of juvenile systemic lupus erythematosus (JSLE) varies between ethnic groups and countries. Previous nationwide population-based or cohort studies of JSLE demonstrated higher rates in non-White populations, Asian, and African American populations (Supplementary Data 1, available from the authors on request). They reported an incidence of JSLE from 0.36 to 2.5 per 100,000 persons and a prevalence of 1.89 to 25.7 per 100,000 persons[1,2].

A few JSLE data were reported indirectly as a small fraction of the epidemiological data of adult SLE, categorized by 10-year age groups[2,3,4]. Moreover, the majority of studies in Korea have focused on those of adult SLE[3,5].

This study aimed to investigate the prevalence and incidence of JSLE in the Korean population in 2017 based on national claims data.

MATERIALS AND METHODS

The data were collected from the exclusive National Health Insurance Claims Database, managed by the Health Insurance Review and Assessment (HIRA) service in South Korea. HIRA assesses the quality of healthcare services provided to patients and reviews the medical fees for reimbursement decisions in partnership with the National Health Insurance Service (NHIS). The Korean NHIS, developed in 1989, manages over 97.7% of the population, which is about 50 million[6,7].

The study participants included all patients who had JSLE as a primary or secondary diagnosis in an outpatient visit or a hospital admission from January 1, 2016, to December 31, 2017. JSLE was identified using the diagnostic code M32 from the Korean Standard Classification of Diseases.

JSLE cases, which are registered in the copayment assistance policy for rare, incurable diseases by NHIS in South Korea[7], were identified as true and accurate cases. To register the patient in this copayment assistance policy, a rheumatologist must confirm their diagnosis and apply on their behalf. The patients must meet at least 4 of the American College of Rheumatology (ACR) classification criteria revised in 1997 to satisfy the reimbursement policy of the NHIS[8]. Registration and copayment for a rare, incurable disease is strictly regulated by the Ministry of Health and Welfare, and the possibility of misclassification can be minimized by this process.

We collected data from patients of both sexes, from ages 0 to < 18 years. The patients had at least 1 claim for a JSLE diagnosis, and the first visit date for JSLE was obtained. This study was approved by the Institutional

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The prevalence of JSLE in 2017 was calculated using the number of affected cases during the year divided by the total population, presented as cases per 100,000 persons. Data on the total South Korean population were estimated from the midyear resident registration population in 1-year age groups in 2017, available from the Korean Statistical Information Service (http://kosis.kr).

The incidence of JSLE was calculated using the number of new incident cases during the year divided by the total population of the year, presented as cases per 100,000 person-years (PY). Incident cases were defined as patients newly diagnosed with JSLE during 2017.

In both sexes, the annual age-specific prevalence and incidence were analyzed. We used a change-point simulation to find the age at which changes in prevalence and incidence occurred

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc.) and IBM SPSS statistics 19.0 (IBM Corp.). A change-point analysis was conducted using R statistical software (www.r-project.org). A value $P < 0.05$ was considered statistically significant.

RESULTS

We analyzed the JSLE patients between 5 and 18 years old, as the claim data cannot identify a medical record of patients under 5 years (13 prevalent cases and 11 incident cases), which may be assumed as maternal SLE or neonatal SLE. There were 447 prevalent JSLE patients (93 males, 354 females) and 178 incident JSLE patients (45 males, 133 females).

The prevalence of JSLE was 6.92 (95% CI 6.90–6.94) per 100,000 persons (Table 1). The incidence of JSLE was 2.76 (95% CI 2.75–2.77) per 100,000 PY (Table 2).

We estimated the sex- and age-specific prevalence and incidence of JSLE during the period; these were higher in females than in males. There was a marked increase in females during the period of adolescence. The difference between males and females was less prominent in very early–onset JSLE.

The prevalence of JSLE in males and females was 2.78 (95% CI 2.76–2.80) per 100,000 male population and 11.37 (95% CI 11.34–11.41) per 100,000 female population. The incidence of JSLE in males was 1.35 (95% CI 1.33–1.36) per 100,000 male population, and 4.27 (95% CI 4.25–4.30) per 100,000 female population.

According to the change-point analysis, we found that the incidence and prevalence of female patients increased rapidly at the ages of 14 and 15 years, respectively (Figure 1). The sensitivity analysis using different age intervals of 2–5 years showed that the inflection points were within the same age interval (Supplementary Data 2, available from the authors on request). There was no significant change point by age in male patients.

DISCUSSION

Compared to population-based pediatric studies in other countries, the incidence of JSLE in this study was comparable with the United States (2.22–2.5 per 100,000) and higher than in the UK (0.73 per 100,000)[2,9]. The prevalence of JSLE was lower than in the US (9.73–12.6 per 100,000)[2,9].

In terms of race, the incidence of JSLE among Asians in the UK (0.8–2.5 per 100,000), US (1.61–4.16 per 100,000), and New Zealand (1.17 per 100,000) was similar to that of this study[9,10,11]. The incidence of White patients in the UK (0.1 per 100,000) and US (0.5–1.33 per 100,000) were lower than in this study[2,9,10,11,12,13]. The prevalence of JSLE in Taiwan was 6.3 per 100,000 persons, similar to this study[14]. The prevalence of JSLE in White patients in the US (0.7–4.86 per 100,000 persons) was lower, and that of the Asia Pacific (18.3–25.7 per 100,000 persons) and African American (18.4 per 100,000 persons) populations in the US was higher than our results[2,9,10,11,12,13,15]. In light of the difference in ethnic proportions, we need to be more cautious in interpreting epidemiologic findings.

Through analysis of data categorized in 1-year age groups, a significant increase in the incidence and prevalence rates was seen in females with JSLE; this increase was not apparent in the males with JSLE. Change-point analysis of the incidence and prevalence of JSLE (Figure 1) showed that the change point occurred at 14 years for incidence and 15 years for prevalence.

Table 1. Prevalence of JSLE.

Age, yrs	Overall			Male			Female		
	N	Population	Rate (95% CI)	N	Population	Rate (95% CI)	N	Population	Rate (95% CI)
Overall	447	6,455,854	6.92 (6.90–6.94)	93	3,342,952	2.78 (2.76–2.80)	354	3,112,902	11.37 (11.34–11.41)
5	1	482,297	0.21 (0.20–0.22)	1	247,529	0.40 (0.38–0.43)	0	234,769	–
6	3	474,368	0.63 (0.61–0.66)	1	244,012	0.41 (0.38–0.44)	2	230,356	0.87 (0.86–0.91)
7	5	460,372	1.09 (1.06–1.12)	2	237,194	0.84 (0.81–0.88)	3	223,178	1.34 (1.30–1.39)
8	7	457,979	1.53 (1.49–1.56)	2	235,772	0.85 (0.81–0.89)	5	222,207	2.25 (2.19–2.31)
9	11	481,854	2.28 (2.24–2.33)	4	247,880	1.61 (1.56–1.66)	7	233,975	2.99 (2.92–3.06)
10	12	472,317	2.54 (2.50–2.59)	4	243,522	1.64 (1.59–1.69)	8	228,795	3.5 (3.42–3.57)
11	20	442,524	4.52 (4.46–4.58)	4	229,015	1.75 (1.69–1.80)	16	213,509	7.49 (7.38–7.61)
12	26	454,656	5.72 (5.65–5.79)	7	235,616	2.97 (2.90–3.04)	19	219,040	8.67 (8.56–8.79)
13	32	483,215	6.62 (6.55–6.69)	7	250,765	2.79 (2.73–2.86)	25	232,450	10.76 (10.63–10.88)
14	43	493,510	8.71 (8.63–8.79)	12	257,027	4.67 (4.59–4.75)	31	236,483	13.11 (12.97–13.25)
15	50	526,372	9.5 (9.42–9.58)	10	274,449	3.64 (3.57–3.71)	40	251,923	15.88 (15.74–16.02)
16	95	598,289	15.88 (15.79–15.97)	14	312,162	4.48 (4.41–4.56)	81	286,127	28.31 (28.14–28.47)
17	142	628,104	22.61 (22.50–22.71)	25	328,012	7.62 (7.53–7.71)	117	300,092	38.99 (38.81–38.99)

JSLE: juvenile systemic lupus erythematosus.

Table 2. Incidence of JSLE.

Age, yrs	Overall			Male			Female		
	Cases, n	Population	Rate (95% CI)	Cases, n	Population	Rate (95% CI)	Cases, n	Population	Rate (95% CI)
Overall	178	6,455,854	2.76 (2.75–2.77)	45	3,342,952	1.35 (1.33–1.36)	133	3,112,902	4.27 (4.25–4.30)
5	1	482,297	0.21 (0.19–0.22)	1	247,529	0.40 (0.38–0.43)	0	234,769	–
6	2	474,367	0.42 (0.40–0.44)	1	244,011	0.41 (0.38–0.44)	1	230,356	0.43 (0.41–0.46)
7	4	460,369	0.87 (0.84–0.90)	2	237,193	0.84 (0.81–0.88)	2	223,176	0.90 (0.86–0.94)
8	4	457,974	0.87 (0.85–0.90)	2	235,770	0.85 (0.81–0.89)	2	222,204	0.90 (0.86–0.94)
9	5	481,847	1.04 (1.01–1.07)	1	247,878	0.40 (0.38–0.43)	4	233,970	1.71 (1.66–1.76)
10	6	472,306	1.27 (1.24–1.30)	2	243,518	0.82 (0.79–0.86)	4	228,788	1.75 (1.70–1.80)
11	11	442,512	2.49 (2.44–2.53)	3	229,011	1.31 (1.26–1.36)	8	213,501	3.75 (3.67–3.83)
12	10	454,636	2.20 (2.16–2.24)	2	235,612	0.85 (0.81–0.89)	8	219,024	3.65 (3.57–3.73)
13	14	483,189	2.90 (2.85–2.94)	2	250,758	0.80 (0.76–0.83)	12	232,431	5.16 (5.07–5.25)
14	21	493,478	4.26 (4.20–4.31)	7	257,020	2.72 (2.66–2.79)	14	236,458	5.92 (5.83–6.02)
15	24	526,329	4.56 (4.50–4.62)	4	274,437	1.46 (1.41–1.50)	20	251,892	7.94 (7.83–8.05)
16	37	598,239	6.18 (6.12–6.25)	9	312,152	2.88 (2.82–2.94)	28	286,087	9.79 (9.68–9.90)
17	39	628,009	6.21 (6.15–6.27)	9	327,998	2.74 (2.69–2.80)	30	300,011	10.0 (9.89–10.11)

JSLE: juvenile systemic lupus erythematosus.

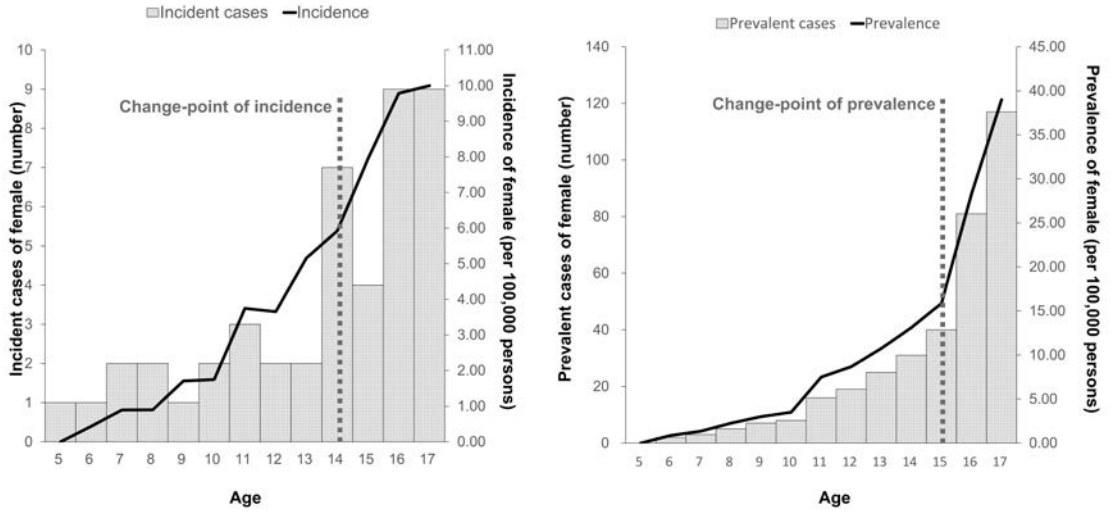

Figure 1. Change point of incidence and prevalence in female patients with JSLE. According to the change-point analysis, we found that the incidence (left) and prevalence (right) of female patients increased rapidly at the ages of 14 and 15 years, respectively.

This result can be supported by a previous report that the mean age at menarche of Korean adolescents is 12.7 years, and overall 95.8% of the girls experienced menstruation before 15.0 years old[16]. A high incidence rate in patients under 3 years needs to be inspected more cautiously. There are possibilities of neonatal or monogenic causes of SLE[17]. However, we cannot identify a medical record of every single patient.

In the present study, the prevalence and incidence of JSLE were higher in females than in males, and there was a marked increase in females after adolescence. In many studies, there is clear sex predominance in SLE, affecting more females of child-bearing age[4,17,18,19]. Many clinical and experimental studies have suggested that sex bias in autoimmune diseases such as JSLE may be influenced by sex hormones and sex chromosomes. Because sex bias in autoimmune diseases is stronger post puberty, hormones can initiate or exaggerate the autoimmune process. The female sex hormones estrogen and prolactin are considered to influence the immune response and modulate their coordinated response, such as allowing the survival of autoreactive B cells and skewing their maturation[17,19]. Sex chromosomes may affect autoimmune disease through differences in X chromosome gene expression, X chromosome gene dosage, and Y chromosome expression[17,19].

A limitation of using National Health Insurance claim data is that there is no information on JSLE patients who have not visited a medical institution, and the diagnostic information may be inaccurate due to simple coding errors, classification errors due to lack of medical knowledge, and reimbursement system procedures. Further, our dataset does not include a rate of lupus nephritis or mortality cases that might be important prognostic information.

Despite these issues, national health insurance claims data covering almost the entire population can provide a meaningful, nationally representative study of small populations, such as children or those with rare diseases. Moreover, the use of physician-confirmed diagnoses of SLE according to the ACR criteria using the copayment system data might be a definite strength of this study. In addition, as the Korean and Taiwanese adult SLE epidemiological studies using health insurance data showed similar epidemiologic profiles[3,20], our results can be compared to those reported in Taiwan using health insurance data.

In conclusion, there were 4 main findings from this study: The prevalence of JSLE was 6.92 per 100,000 persons; the incidence of JSLE was 2.76 per 100,000 PY; the prevalence and incidence of JSLE were higher in females than in males; and 14 and 15 years of age in females were identified as change point in incidence and prevalence, respectively. In epidemiologic studies in childhood, it might be more important to investigate a rate in smaller age interval rather than a 10-year interval, due to a small number of patients and various change points within the developmental stage.

REFERENCES

1. Klein-Gitelman M, Lane JC. Systemic lupus erythematosus. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. Textbook of Pediatric Rheumatology. 7th ed. Philadelphia: Elsevier, Inc; 2016: 285-317.
2. Pineles D, Valente A, Warren B, Peterson MG, Lehman TJ, Moorthy LN. Worldwide incidence and prevalence of pediatric onset systemic lupus erythematosus. Lupus 2011;20:1187-92.
3. Shim JS, Sung YK, Joo YB, Lee HS, Bae SC. Prevalence and incidence of systemic lupus erythematosus in South Korea. Rheumatol Int 2014;34:909-17.
4. Stojan G, Petri M. Epidemiology of systemic lupus erythematosus: an update. Curr Opin Rheumatol 2018;30:144-50.
5. Ju JH, Yoon SH, Kang KY, Kim IJ, Kwok SK, Park SH, et al. Prevalence of systemic lupus erythematosus in South Korea: an administrative database study. J Epidemiol 2014;24:295-303.
6. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 2017;32:718-28.
7. National Health Insurance Service. National health insurance & long-term care insurance system in Republic of Korea. [Internet. Accessed October 20, 2020.] Available from: www.nhis.or.kr/static/html/wbd/g/a/wbdga0704.html
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
9. Hiraki LT, Feldman CH, Liu J, Alarcón GS, Fischer MA, Winkelmayer WC, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis Rheum 2012;64:2669-76.
10. Watson L, Leone V, Pilkington C, Tullus K, Rangaraj S, McDonagh JE, et al. Disease activity, severity, and damage in the UK Juvenile-Onset Systemic Lupus Erythematosus Cohort. Arthritis Rheum 2012;64:2356-65.
11. Concannon A, Rudge S, Yan J, Reed P. The incidence, diagnostic clinical manifestations and severity of juvenile systemic lupus erythematosus in New Zealand Maori and Pacific Island children: the Starship experience (2000-2010). Lupus 2013;22:1156-61.
12. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002-2004: The Georgia Lupus Registry. Arthritis Rheumatol 2014;66:357-68.
13. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Shenvi N, et al. The Georgia Lupus Registry: a population-based estimate of the incidence and prevalence of childhood-onset SLE [abstract]. In: Proceedings of 2009 ACR Annual Scientific Meeting, 2009, October 16-21; Philadelphia: American College of Rheumatology; 2009:573-5.
14. Huang JL, Yao TC, See LC. Prevalence of pediatric systemic lupus erythematosus and juvenile chronic arthritis in a Chinese population: a nation-wide prospective population-based study in Taiwan. Clin Exp Rheumatol 2004;22:776-80.
15. Kurahara DK, Grandinetti A, Fujii LL, Tokuda AA, Galario JA, Han MJ, et al. Visiting consultant clinics to study prevalence rates of juvenile rheumatoid arthritis and childhood systemic lupus erythematosus across dispersed geographic areas. J Rheumatol 2007;34:425-9.
16. Lee MH, Kim SH, Oh M, Lee KW, Park MJ. Age at menarche in Korean adolescents: trends and influencing factors. Reprod Health 2016;13:121.
17. Chiaroni-Clarke RC, Munro JE, Ellis JA. Sex bias in paediatric autoimmune disease - not just about sex hormones? J Autoimmun 2016;69:12-23.
18. Chiu YM, Lai CH. Nationwide population-based epidemiologic study of systemic lupus erythematosus in Taiwan. Lupus 2010;19:1250-5.
19. Zandman-Goddard G, Peeva E, Shoenfeld Y. Gender and autoimmunity. Autoimmun Rev 2007;6:366-72.
20. Yeh KW, Yu CH, Chan PC, Horng JT, Huang JL. Burden of systemic lupus erythematosus in Taiwan: a population-based survey. Rheumatol Int 2013;33:1805-11.