[Title page]

Full title of manuscript (maximum of 20 words):

Incidence and prevalence of juvenile systemic lupus erythematosus in Korea: data from the national health claims database 2017

Complete given names and surnames of all authors with ORCID ID :

Sang Gyu Kwak (ORCID : 0000-0003-0398-5514) [1]

Sung-Hoon Park (ORCID : 0000-0002-3218-5420) [2]

Ji Yoon Kim (ORCID : 0000-0002-5577-6629) [3]

Sang Gyu Kwak and Sung-Hoon Park contribute equally as a first author.

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Name of department(s) and institution(s) to which the work should be attributed:

[1]Department of Medical Statistics, Catholic University of Daegu School of Medicine, Daegu, Republic of Korea

[2]Division of Rheumatology, Department of Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, Republic of Korea

[3]Department of Pediatrics, School of Medicine, Kyungpook National University, Daegu, Republic of Korea

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Initials, surnames, appointments, and highest academic degrees:

S. G. Kwak, PhD

S. Park, MD, PhD

J. Y. Kim, MD, PhD

Name, address, and e-mail of author responsible for correspondence:

Ji Yoon Kim, MD, PhD.

Department of Pediatrics, Kyungpook National University Hospital, 130 Dongdeok-Ro, Jung-Gu, Daegu, 41944, Republic of Korea. E-mail: phojyk@knu.ac.kr

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[Abstract]

Objective: The purpose of the present study was to investigate the prevalence and incidence of 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 one 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 one time, any type of medical services as a diagnostic code of M32 were selected. For incident cases, patients who did not use medical services during prior 1 year as M32 code and newly registered in 2017 were defined. Statistical analysis was used to find the age at which changes in prevalence and incidence occurred, that is, change-point.

Result: The prevalence of JSLE was 5.35 per 100,000 persons and the incidence of JSLE was 2.20 per 100,000 person-year 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, 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.

[Manuscript Body]

Introduction

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-Caucasian populations, Asian, and African-American populations (Supplement1). 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 was reported indirectly as a small fraction of the epidemiological data of adult SLE, categorized by 10-year age groups[2-4]. 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 claim data.

Patients 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 number 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 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 co-payment assistance policy for rare-incurable diseases by NHIS in South Korea[7], were identified as true and accurate JSLE cases. To register the patient in this co-payment assistance policy, a rheumatologist must confirm the diagnosis and apply on behalf of their patient. The patients must meet at least four of the American college of rheumatology (ACR) classification criteria revised in 1997 to satisfy the reimbursement decision policy of the NHIS[8]. Registration and co-payment of rare-incurable disease is strictly regulated by the ministry of health and welfare. The possibility of misclassification can be minimized by this process.

We collected data from patients under 18 years old (0-17.99 ages) and both sexes. The patients had at least one claim for a JSLE diagnosis, and the first visit date for JSLE was obtained. This study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (KNUCH 2017-12-029).

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 one-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-year. Incident cases were defined as patients newly diagnosed with JSLE during 2017.

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

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS statistics 19.0 (IBM Corp., Armonk, NY, USA). A change-point analysis was conducted using R statistical software (http://www.r-project.org). A p-value < 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 very young patients under 5 (13 prevalent cases and 11 incident cases), which may be assumed 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 (95% CI) was 6.92 (6.90–6.94) per 100,000 persons (Table1). The incidence of JSLE (95% CI) was 2.76 (2.75–2.77) per 100,000 person-year (Table2).

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

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

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, respectively (Figure1). The sensitivity analysis using different age intervals of 2-5 years of age showed the inflection points were within the same age interval (Supplement2). 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 USA (2.22~2.5 per 100,000) and higher than in UK (0.73 per 100,000)[2, 9]. The prevalence of JSLE was lower than in USA (9.73~12.6 per 100,000) [2, 9].

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

Through analysis of data categorized by one-year of age, a significant increase in the incidence and prevalence rates were seen in females with JSLE, which 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 old for incidence and 15-years old for prevalence. This result can be supported by the recent 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]. High incidence rate in patients under 3 year-old age need to be inspected more cautiously. There are possibilities of neonatal or monogenic causes of lupus[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 women than in men and there was a marked increase in females after adolescence. In many studies, there is clear sex predominance in SLE, affecting more females of childbearing age[4, 17-19]. 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. As 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]. Apart from sex hormones, 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. Furthermore, our dataset does not include a rate of lupus nephritis or mortality case that might be an 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 per the ACR criteria using the co-payment 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 four 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 person-year, the prevalence and incidence of JSLE were higher in females than in males, and 13-years-old and 16-years-old in females were identified as change-point ages in incidence and prevalence, respectively. In epidemiologic study in childhood age, it might be more important to investigate a rate in smaller age interval rather than 10-year interval, due to small number of patients and various change points within developmental stage.

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[Figure Legends]

Figure 1. Change-point of incidence and prevalence in female JSLE patients.

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, respectively.

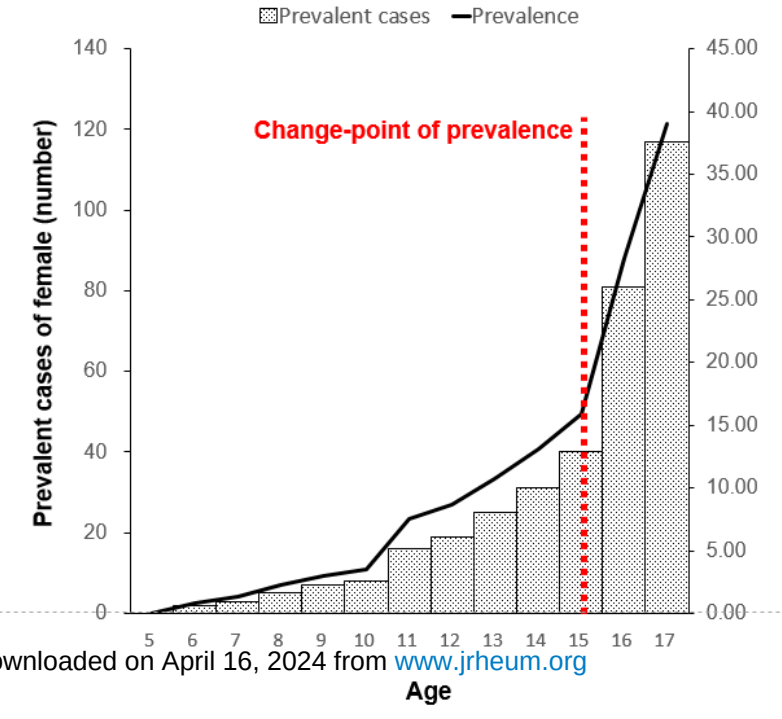

Table 1. Prevalence of JSLE.

Age (yr)	Overall			Male			Female		
	No.	Population	Rate (95% CI)	No.	Population	Rate (95% CI)	No.	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)

Abbr. JSLE, juvenile systemic lupus erythematosus; yr. year; n, number; CI, Confident Interval

Table 2. Incidence of JSLE.

Age (yr)	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)

Abbr. JSLE, juvenile systemic lupus erythematosus; yr. year; n, number; CI, Confident Interval