Association of influenza infection with hospitalisation-related systemic lupus erythematosus flares: a time series analysis

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Abstract

Objective

This study aimed to investigate whether the influenza annual outbreak in Korea is related to hospitalisation-related flares in systemic lupus erythematosus (SLE) patients.

Methods

The weekly frequency of hospitalisation-related SLE flares (2012–2015) was collected from the Korean National Health Insurance claim database. The weekly laboratory-confirmed detection rate of influenza infection was obtained from the Korea Centers for Disease Control and Prevention database. A generalised linear model was used to examine the relative risks (RRs) of hospitalisation-related SLE flares associated with influenza infection, after adjusting for time trends and meteorological data.

Results

A total of 2,223 hospitalisation-related SLE flares were analysed. An interquartile range (24.5%) increase in influenza infection was associated with a 14.0% increase in hospitalisation-related SLE flares (RR, 1.14; 95% confidence interval [CI]: 1.04–1.25; p=0.006). In addition, influenza infections at lag 0–1 (over 2 weeks including concurrent and 1 previous week) and lag 0–2 (over 3 weeks including concurrent and 2 previous weeks) were associated with increase in hospitalisation-related SLE flares (RR, 1.14; 95% confidence interval [CI]: 1.03–1.26; p=0.014 and RR, 1.13; 95% CI: 1.02–1.26; p=0.023). Significant associations were especially observed in women (RR, 1.15; 95% CI: 1.15–1.16; p=0.006) and immunosuppressant (RR, 1.26; 95% CI: 1.26–1.27; p<0.001) or glucocorticoid recipients (RR, 1.17, 95% CI: 1.16–1.17; p=0.004).

Conclusion

This study shows a significant association between seasonal influenza infection and flares in SLE patients, which suggests influenza can be a novel environmental risk factor for SLE flares.

Key words

influenza, systemic lupus erythematosus, flares

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterised by numerous autoantibodies against nucleic acids (1). The majority of patients with SLE have an excessive production of type I interferons (IFNs), which play an important role in the aetiopathogenesis of the disease (2). Normally, the type I IFN system is activated to defend against virus infections and is terminated after eradicating the pathogen (3). In SLE, however, ongoing production of type I IFN by plasmacytoid dendritic cells (pDCs) is stimulated by endogenous nucleic acids. Genetic factors and environmental factors contribute to the dysregulated type I IFN system. For example, type I IFN-regulated genes are overexpressed in patients with SLE (4). In addition, virus infections, one of the possible environmental factors, could increase the production of type I IFN after pattern recognition receptors sense viral nucleic acids (5).

It has been suggested that viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19 can trigger SLE. Despite this, a few studies have investigated the potential association between viral infections and SLE flares. EBV infection is associated with SLE flares, independent of immunosuppressants (6). Other case series studies have reported on the possibility of a CMV infection as a trigger for SLE (7, 8). Recently, Sun *et al*. explored the association between varicella zoster virus infection and disease flares. This matched cohort study found a 3–4 times higher risk for flares in patients with SLE than in controls (9).

Influenza infection is common (10) and is reported to be associated with autoimmune diseases such as coeliac disease (11) and Guillain-Barré syndrome (12). In addition, immunocompromised patients are at higher risk for influenza infection and an annual influenza vaccination is recommended (13-15). Chang *et al*. reported that influenza vaccinations reduce hospitalisation rates, intensive care unit (ICU) admissions, and mortality in patients with SLE (15). However, the effect of influenza infection itself on disease activity in patients with SLE has not yet been demonstrated.

Thus, this study hypothesised that influenza infection could trigger flares in patients with SLE. We conducted for the first time, to our knowledge, a time series analysis to examine whether ambient influenza infections are associated with the risk of hospitalisation-related SLE flares, using a large Korean population-based cohort and well-established surveillance system for influenza infections.

Methods

Ethnic statement

This study protocol was approved by the Institutional Ethics Review Board of St. Vincent's Hospital, Catholic University of Korea.

Data sources

We obtained claims data for population-based SLE for 2011–2015 from the Korean national healthcare insurance database (NHID). Korea built the foundation of its National Health Insurance (NHI) following the Medical Insurance Act of 1963. Korea provided health insurance coverage of its entire population of over 50 million in 1989. Health research that used NHI claims data started in 1986, and the National Health Insurance Database (NHID) was formed in 2012. The healthcare utilisation database is the largest component of the NHID, and is based on data collected during health care service claims. This information includes inpatient and outpatient healthcare service usage (diagnosis, length of stay, treatment costs, services received) and prescription records (drug code, days prescribed, daily dosage).

The 2012–2015 data were used for identifying cases of SLE flares. The 2011 data were only used to obtain baseline medication information of patients hospitalised for SLE flares in 2012 as baseline medication was investigated during -1 to -90 days before admission considering that SLE patients taking medication usually visit at least once every three months.

Definition of SLE and hospitalisation-related SLE flares

The algorithm for identifying SLE using claims data was reported in Korea

previously by Shim *et al*. (16) In accordance with Shim *et al*. (16), we defined patients with SLE as those with a combination of a diagnostic Internal Classification of Disease (ICD) – 10 code of M32 and one of the following claims: at least one hospitalisation or at least one concomitant use of hydroxychloroquine and immunosuppressant, or at least two times tests for anti-dsDNA antibody or complement (C3•C4). The earliest date of a medical claim among the four aforementioned characteristics was defined as the index date for patients with SLE. These SLE cohort included both the prevalent SLE and incident SLE. Among the patients with SLE, patients younger than age one (12 months) were excluded from the analysis. Patients who were hospitalised within four weeks of a previous hospitalisation for flares were excluded because we considered the repeat hospitalisation to be due to uncontrolled disease activity, and not a new flare.

Since claims data do not provided measurable disease activity assessment such as SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), SLAM (Systemic Lupus Activity Measure), SFI (SELENA-SLEDAI Flare Index) and BILAG (British Isles Lupus Assessment Group), we used an alternative method to speculate the disease activity. Since all flare cases cannot be estimated, we narrowed down our scope to the cases requiring hospitalisation and glucocorticoid treatment. We used "hospitalisation-related flare" as an outcome assessment variable. Among these SLE, those who were hospitalised for more than 2 days and prescribed glucocorticoid ≥20 mg/day were defined as having "hospitalisation-related SLE flares". When SLE patient is admitted to a hospital and at the same time receives medium to high-dose steroid treatment, claims data allows to distinguish SLE flare from other concomitant diseases by applying different main disease codes. Therefore, it is defined that the status, requiring medium to high doses dose of steroids with hospitalisation for more than 2 consecutive days, is related to flare of SLE. The weekly number of patients hospitalised for SLE flares was counted between 2012–2015.

Influenza virus data

The weekly detection rate of influenza viruses in the general population, not in SLE patients, between 2012–2015 was obtained from the Korea Centers for Disease Control and Prevention (KCDC). For a long time, KCDC has been running a surveillance system to detect the major respiratory viruses including influenza virus that can represent Korea. The territory of South Korea is relatively small (100,032 km^2) and divided into 17 administrative districts. KCDC has designated two sentinel hospitals in each administrative district except one (four hospitals in one district) for respiratory virus surveillance. A total number of sentinel hospitals located nation-wide is 36 until 2015 and extended to 54 since 2016. Nasopharyngeal specimens from patients with acute respiratory symptoms were collected at sentinel hospitals and subjected to respiratory virus testing via multiplex polymerase chain reaction (PCR). The results of this surveillance (detection rate of respiratory virus) has been reporting each week on their website (17). Detection rate of influenza virus was calculated as a proportion of patients who is confirmed for influenza viral infection by PCR among the those with acute respiratory viral infection symptoms who visited sentinel hospitals and represented to percentage (%).

Potential confounders

A time-series analysis has to control for seasonality. Additionally, factors with seasonal variability should be considered potential confounders. Since influenza infections peak in winter, factors related to influenza infection detection – such as temperature and humidity – should also be considered potential confounders. Without adjustment for potential confounders, the association between some meteorological factors and hospitalisation-related SLE flares can appear as an association between influenza infection and SLE flares.

Data pertaining to potentially confounding factors regarding influenza virus detection rates were obtained from public websites. We obtained hourly meteorological data for temperature, humidity, solar radiation, and cloud amount from the Korea Meteorological Administration website. The hourly means of all variables were calculated using the obtained raw data in each station and converted to daily means. Next, the daily metrological data were converted into weekly means and analysed in conjunction with the influenza infection data. For meteorological data, there were missing data less than 1%, which were replaced by the average mean value.

Subgroup analysis

A time series analysis does not allow adjustment for single measured variables such as age and medications. It only allows for analysis of regular (hours, day, or week, etc.), repeatedly measured variables such as temperature and humidity. Thus, previously known risk factors for flares such as disease activity and immunosuppressants could not be adjusted on an individual level. Instead, we conducted a subgroup analysis based on possible confounding factors commonly collected as claims data. This included age, sex, the use of immunosuppressants, and the use of glucocorticoid. Patients were divided into three groups based on age, and considering child-onset SLE and elderly-onset SLE (<16 *vs*. 17–49 *vs*. ≥50) (18-20). Immunosuppressants included cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, cyclosporin, tacrolimus, and hydroxychloroquine, except for glucocorticoid. We also investigated the use of glucocorticoid apart from immunosuppressive agents.

Statistical analysis

Generalised additive modelling (GAM) (21) with semi-parametric estimation was used to visualise a relationship between influenza viruses and hospitalisation-related SLE flares. We estimated the effect of the weekly average detection rate of influenza virus on the weekly number of hospitalisation-related SLE flares using generalised linear models (GLM) with Poisson distribution. We adjusted for weekly mean values of temperature, relative humidity, solar radiation, and cloud amount, which could affect the seasonality of

influenza virus. We additionally controlled for seasonality using sequential number of weeks (1–104).

The degrees of freedom (*df*) for each confounding factor were determined based on the unbiased risk estimation derived from the GAM. Potential confounders used in the model were mean temperature with 8 *df*, mean relative humidity with 4 *df*, solar radiation with 1 *df*, mean cloud amount with 2 *df* and 4 *df* per year (4 *df* × 2 years = 8 *df*) for seasonality.

Moving average of influenza infection rate and confounding variables were used to regress hospital admission counts due to SLE flares in the GLM. The effect was expressed as relative risk in SLE patient counts associated with an interquartile range (IQR) increase in influenza infection rate. To consider delayed and cumulative effects of influenza infections on hospitalisation-related SLE flares, we took moving average of each covariate for 8 weeks. For example, "lag 0-8" for influenza infection refers to a moving average of influenza infection rate over 8 weeks including concurrent week and 7 previous weeks.

SAS statistical software (v. 9.4; SAS Institute, Cary, NC, USA) was used for data collation. All statistical analyses were performed using R software (v. 3.5.1; The R Project for Statistical Computing, www.r-project.org). A *p*-value <0.05 was considered statistically significant.

Results

From January 2012 to December 2015, there were 2,223 hospitalisation-related SLE flares among 1,799 SLE patients. Of these, 1,551 (86.2%) were women, and the mean age at hospitalisation due to SLE flares was 35.8 (SD 14.4) years. The baseline characteristics of patients hospitalised for SLE flares are presented in Table I.

Association of ambient influenza infection with hospitalisation-related SLE flares

The weeks with higher detection rates of influenza infection in the general population had higher numbers of hospitalisation-related SLE flares (Fig. 1).

Table I. Baseline characteristics of patients hospitalised with SLE flare-up (2012–2015).

	Total n=1,799*
Age	
Mean value	35.8 ± 14.4
<16	67 (3.7)
16–49	1,407 (78.2)
≥50	325 (18.1)
Sex	
Women	1,551 (86.2)
Men	248 (13.8)
Type of institutions	
Tertiary hospitals	1,770 (98.4)
General hospitals and others	29 (1.6)
Medication†	
Immunosuppressants	
Cyclophosphamide	8 (0.4)
Oral	8 (0.4)
Intravenous‡	0 (0.0)
Mycophenolate mofetil	145 (8.1)
Methotrexate	62 (3.5)
Azathioprine	140 (7.8)
Cyclosporine	70 (3.9)
Tacrolimus	76 (4.2)
Hydroxychloroquine	667 (37.1)
Glucocorticoid	1,344 (74.7)

*There were 2,223 admissions for SLE flares in 1,799 SLE patients.
†Considering that SLE patients taking medication usually visit at least once every three months, medication was investigated during -1 to -90 days before admission.
‡To avoid duplication of lupus nephritis patients who have been undergone cyclophosphamide induction treatment, patients who have intravenous cyclophosphamide prescription during -1 to -90 days before admission was excluded in the study. This allows including only lupus nephritis patients who start the 1st intravenous cyclophosphamide induction therapy at or after enrolment.
SLE: systemic lupus erythematosus.

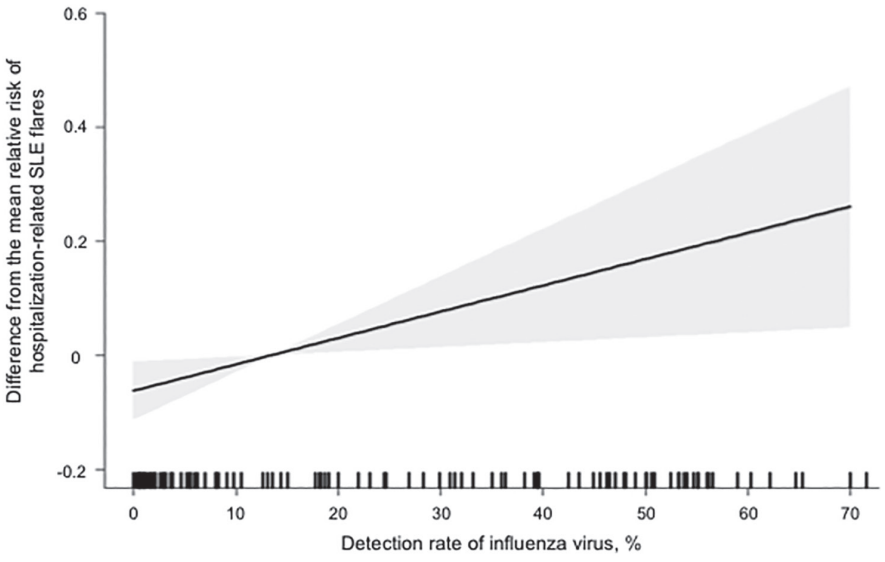

Fig. 1. Effects of ambient influenza infections on hospitalisation-related SLE flares. The x- and y-axes represent the weekly virus detection rate as a percentage and difference from the mean log relative risk of hospitalisation-related SLE flares, respectively. Solid lines represent associations between the weekly virus detection rate and weekly number of hospitalisation-related SLE flares and grey area represent 95% confidence intervals for the risk.

At lag 0, IQR (24.5%) increase in influenza infection rate was associated with a 14.0% (relative risk [RR], 1.14; 95% confidence interval [CI]: 1.04–1.25; *p*=0.006) higher rate of hospitalisation-related SLE flares in adjusted models (Table II). This positive association between influenza infection and hospital-

isation-related SLE flares was also observed in lag 0–1 and lag 0–2 (Fig. 2). An IQR increase in the detection rate of influenza infection at lag 0–1 and lag 0–2 was associated with 13.6% (RR, 1.13; 95% CI: 1.03–1.26; p=0.014) and 13.2% (RR, 1.13; 95% CI: 1.02–1.26; *p*=0.023) higher rates of hospitalisation-related SLE flares, respectively (Table II).

Effect modification by age, sex, immunosuppressants, and glucocorticoid

The effect modification by age, sex, immunosuppressants, and glucocorticoid on the association between influenza infection rate in the general population and hospitalisation-related SLE flares are shown in Table III. Hospitalisation-related SLE flares among the aged 16–49 years was significantly associated with influenza infection rate in general population, not influenza in SLE patients. ($p<0.05$). Those aged <16 years or ≥50 years showed no association between flares and influenza infection. A significant association was found in women (RR, 1.15; 95% CI: 1.145–1.155; *p*=0.006), but not in men (*p*=0.494). The association of the detection rate for influenza virus with the number of hospitalisation-related SLE flares was also significant among those treated with immunosuppressants (RR, 1.26; 95% CI: 1.26–1.27; $p<0.001$) regardless of glucocorticoid or glucocorticoid (RR 1.17, 95% CI 1.16–1.17, *p*=0.004) regardless of other immunosuppressants during the 3 months before hospitalisation, but not significant among those not treated with immunosuppressants (*p*=0.757) or glucocorticoid (*p*=0.369).

Table II. Risk of hospitalisation-related SLE flares associated with detection rate of ambient influenza infection.

Lag time, week†	RR in risk (95% CI) per IQR increase in exposure‡	*p*-value
At lag 0	1.140 (1.039, 1.251)	0.006
At lag 0-1	1.136 (1.027, 1.258)	0.014
At lag 0-2	1.132 (1.017, 1.259)	0.023
At lag 0-3	1.109 (0.989, 1.242)	0.077
At lag 0-4	1.098 (0.972, 1.240)	0.134
At lag 0-5	1.099 (0.963, 1.255)	0.162
At lag 0-6	1.108 (0.958, 1.282)	0.167
At lag 0-7	1.033 (0.880, 1.212)	0.692
At lag 0-8	1.067 (0.893, 1.275)	0.476

†The moving average lag was used in this analysis, where "lag 8" for influenza infection refers to a moving average of influenza infection rate over 8 weeks including concurrent week and 7 previous weeks.
‡Adjusted for temperature, humidity, solar radiation, amount of solar exposure, and seasonality.
SLE: systemic lupus erythematosus; OR: odds ratio; CI: confidence interval; IQR: interquartile range.

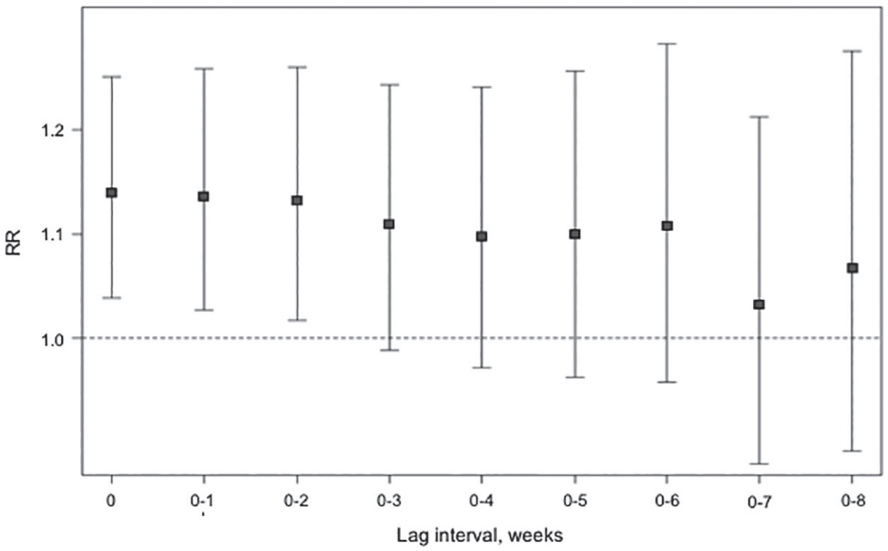

Fig. 2. Time-series analysis of effects of ambient influenza infections on hospitalisation-related SLE flares. Error bars show 95% confidence intervals.

Discussion

This study conducted using a population-based cohort merged with the KCDC database and found the association between ambient influenza infection and hospitalisation-related SLE flares. For each IQR increase in the detection rate of the influenza virus in the general population, there is a 14% increase in the frequency of hospitalisations for SLE flares. Considering that the proportion of influenza infection in seasonal outbreaks increases up to 50–70% among patients with acute respiratory symptoms, the effect of influenza infection on SLE flares is remarkable.

Influenza has been linked to autoimmune disease and is reported to trigger or exacerbate autoimmune diseases, including experimental autoimmune encephalomyelitis (22, 23), coeliac disease (11), and Guillain-Barré syndrome (12). Regarding SLE, Slight-Webb *et al*. reported that influenza A virus infection triggers severe pulmonary inflammation following virus clearance in lupus-prone MRL-Fas^{lpr} mice (24). The mechanisms of influenza infection that exacerbate SLE flares are not well known. One of the possible explanations is cytokine storms after influenza infection. That is, chronic pDC activation and secretion of type I IFNs might be amplified in response to influenza RNA that are internalised through Fc receptors and stimulate TLR7 (3). Another explanation is inappropriate negative feedback of tumor necrosis factor-α (TNF-α) in patients with SLE. Type 1 IFN activation correlates with disease activity and severity in SLE and is known to cross-regulate with TNF-α (3). TNF-α inhibits the generation of pDCs from CD34$^+$ haematopoietic progenitors and suppresses pDC production of IFN-α/β in response to influenza virus (25). The anti-inflammatory effects of immunosuppressants and glucocorticoid could decrease the level of TNF-α in SLE, which might

Table III. Risk of hospitalisation-related SLE flares associated with detection rate of ambient influenza infection by subgroup.

Subgroup	Lag time, week†	RR in risk (95% CI) per IQR increase in exposure‡	*p*-value
Age			
<16	At lag 0	1.062 (0.546, 1.067)	0.860
	At lag 1	0.917 (0.451, 1.862)	0.810
	At lag 2	0.791 (0.371, 1.685)	0.544
16–49	At lag 0	1.140 (1.074, 1.264)	0.014
	At lag 1	1.156 (1.032, 1.300)	0.012
	At lag 2	1.145 (1.016, 1.290)	0.026
≥50	At lag 0	1.051 (0.828, 1.334)	0.681
	At lag 1	1.034 (0.800, 1.340)	0.802
	At lag 2	1.075 (0.821, 1.409)	0.599
Sex			
Women	At lag 0	1.150 (1.145, 1.155)	0.006
	At lag 1	1.153 (1.147, 1.159)	0.027
	At lag 2	1.208 (1.201, 1.215)	0.009
Men	At lag 0	1.092 (1.081, 1.104)	0.494
	At lag 1	1.068 (1.054, 1.083)	0.694
	At lag 2	1.050 (1.035, 1.066)	0.792
Use of immunosuppressants 3 months before hospitalisation regardless of glucocorticoid			
Yes	At lag 0	1.262 (1.255, 1.269)	<0.001
	At lag 1	1.238 (1.229, 1.246)	0.015
	At lag 2	1.313 (1.302, 1.323)	0.006
No	At lag 0	1.020 (1.014, 1.025)	0.757
	At lag 1	0.000 (0.930, 1.025)	0.998
	At lag 2	1.010 (1.030, 1.017)	0.924
Use of glucocorticoid 3 months before hospitalisation regardless of immunosuppressants			
Yes	At lag 0	1.167 (1.162, 1.172)	0.004
	At lag 1	1.196 (1.190, 1.202)	0.007
	At lag 2	1.214 (1.206, 1.221)	0.009
No	At lag 0	1.103 (1.093, 1.113)	0.369
	At lag 1	0.913 (0.904, 0.923)	0.500
	At lag 2	1.022 (1.011, 10.34)	0.878

†The moving average lag was used in this analysis, where "lag 8" for influenza infection refers to a moving average of influenza infection rate over 8 weeks including concurrent week and 7 previous weeks
‡Adjusted for temperature, humidity, solar radiation, amount of solar exposure, and seasonality.
SLE: systemic lupus erythematosus; RR: relative risk; CI: confidence interval; IQR: interquartile range.

interrupt the suppression of pDC overproduction of IFN-α/β by TNF-α in response to the influenza virus.

Significant associations were observed in women and in patients on immunosuppressants. There are two possible explanations for the insignificance of influenza infection in men. The first is a small number of men group and the second is a different immune response between women and men patients with SLE. The number of men with SLE flares is only 248 (13.8%) and may lack power to test that hypothesis. Compared with men, also, it has been known that women have a stronger immunity to pathogens, which is associated with increased severity of disease symptoms (26). A stronger immunity to influenza in women could be prone to trigger SLE flares than men.

Regarding medications, patients using immunosuppressants or glucocorticoid are vulnerable to infections. Considering the pathophysiology of SLE, in addition, the anti-inflammatory effects of immunosuppressants or glucocorticoid would work to decrease the level of TNF-α, which suppresses production of IFN-α/β, and lead to amplify the effect of type 1 IFN on SLE flares (3, 25). For the patients included in the analysis, the prescription rate of hydroxychloroquine was found to be 37%. Patients with hospitalisation-related SLE flares included new cases of SLE (n=433) and prescribed medications were investigated during -1 to -90 days before admission, not any time during follow-up. As we recounted the prescription rate of hydroxychloroquine after exclusion of new cases of SLE were, the prescription rate of hydroxychloroquine reached to 54.8%, similar to the previous well-established cohort studies (27-33).

The current study had some limitations that warrant discussion. First, although the influenza virus data from the KCDC has been used as representative data for South Korea, the influenza virus data was gathered from a sample survey. Thus, the influenza virus data, collected in this fashion, cannot encompass the general population, unlike SLE data. Second, this was an environmental epidemiology study that used a time series analysis; the association between ambient influenza infections and SLE flares has not been investigated at the individual level. Thus, further studies to elucidate the associations between influenza infection and SLE flares in individual patients could be helpful for confirming our findings. Lastly, some potential confounders such as hypocomplementaemia or lupus nephritis were not considered in a stratification analysis. Claims data in South Korea supply the results of laboratory test only in a limited sample of general population, so these factors were not available in this cohort set.

Despite these limitations, the present study has several strengths. This is a nationwide population-based study that demonstrated the relationship of ambient influenza infection on SLE flares for the first time. In addition, the time for the persistent effect of ambient influenza infection on SLE flares was also analysed, which enables clinicians to educate their SLE patients properly and safely.

In conclusion, we reported the association between ambient influenza infection and hospitalisation-related SLE flares. More aggressive monitoring of disease activity of SLE could be required during the influenza season, particularly in women and patients on immunosuppressants or glucocorticoid.

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