Analysis of seasonal tendencies in pediatric Henoch–Schönlein purpura and comparison with outbreak of infectious diseases

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Abstract

Henoch–Schönlein purpura (HSP) is one of the most common vasculitis in children. This study was aimed at identifying seasonal trends and epidemiologic features of pediatric HSP patients through public data to analyze the correlation of HSP and prevalence of a specific respiratory or enteric virus.

We extracted information on pediatric HSP patients categorized into 4 age groups and data on 8 respiratory and 4 enteric viruses were extracted from national data. We used the decomposition of time series analysis and correlation analysis to identify the incidence of HSP and the prevalence of each virus.

From 2013 to 2016, 16,940 patients under the age of 18 were diagnosed with HSP in Korea, 6203 (36.6%) were diagnosed with HSP in middle childhood. Spring had the largest number of patients (5252, 31.0%), and summer had the smallest number of patients (3224, 19.0%). The largest and smallest number of cases occurred in March (1949, 11.5%) and August (959, 5.7%), respectively. However, among the adolescents, more patients were diagnosed in the summer (985, 24.8%) than in the fall (760, 19.1%). The positive detection counts of most viruses showed apparent seasonal variations. Depending on the age group, the epidemic patterns of influenza and rotaviruses were temporally and statistically similar to that of HSP.

We have confirmed that the occurrence of pediatric HSP in Korea shows a seasonal tendency, which is age-dependent and related to exposure to infectious agents and suggest some respiratory or enteric viruses may play an important role in pathophysiology.

Abbreviations: HIRA = Health Insurance Review and Assessment Service, HSP = Henoch–Schönlein purpura, PCR = polymerase chain reaction, RSV = respiratory syncytial virus.

Keywords: child, Henoch–Schönlein purpura, infection, vasculitis

1. Introduction

Henoch–Schönlein purpura (HSP) occurs across all races worldwide and is one of the most common forms of vasculitis in children with 10 to 30 cases reported per 100,000 children under 17 years of age.[1,2] Ninety percent of the cases occur in children <10 years of age, with the average age between 4 and 6 years.[2] HSP in adults is rare than in children but often progresses to a serious condition leading to chronic complications. Its annual incidence is estimated to be 15 cases/100,000 per year in children compared with 1.3 cases/100,000 per year in adults. Skin symptoms occur mainly in the lower extremities or hips, but they can also involve the gastrointestinal tract and kidneys. In acute cases, severe abdominal pain, arthralgia, or proteinuria may develop.[3–5] Complications such as intussusception, perforation, and renal failure may also occur, and an accurate diagnosis is needed at the onset of the disease.[6] Therefore, it is important to determine the timing of an HSP epidemic and identify its causative agents.

Though the etiology of HSP is not clear yet, it is thought to be caused by an immune complex that forms after an infection by a bacteria, virus, or protozoa.[2,7] The most common finding is deposition of IgA, and therefore, HSP is presumed to be a disease mediated by IgA immune complexes.[8] Recent studies have looked into the genetic basis of susceptibility to HSP.[9] It is known that the HLA-B34 and HLA-DRB1*01 alleles are associated with HSP patients.[10,11] Nevertheless, approximately 50% of the patients with HSP have been infected with upper respiratory tract infections and have been reported to be associated with streptococci, adenovirus, parvovirus, and mycoplasma.[7,12,13] Since HSP occurs mainly after an upper respiratory tract infection, it is relatively more frequent in late autumn, winter, and spring when these infections are common, compared with summer.[4,12,13] However, there have been no studies using national health big data showing a direct relationship between HSP and various infectious diseases. In South Korea, HSP is a relatively common disease, but reports on the overall developmental patterns in children and adolescents in recent years are lacking, and only studies that investigate its

epidemiology in individual hospitals are available.[14] Direct comparison between the prevalence of HSP and the incidence of respiratory and enteric infections in South Korea have not been reported.

Therefore, we identified the seasonal trends in HSP occurrence and the epidemiologic features of pediatric HSP patients through the public health data. We also analyzed the correlation between the incidence of HSP occurrence and specific respiratory or enteric viruses in this study.

2. Methods

2.1. Data extraction of pediatric HSP patients

South Korea is responsible for more than 98% of the population's health cover system, and patient assessment and evaluation are managed by the Health Insurance Review and Assessment Service (HIRA).[15] Therefore, the HIRA database contains disease information for almost the entire population of South Korea. Open data are available which does not contain any personal information, through a rigorous screening process for research purposes only. We extracted information on pediatric HSP patients from the HIRA database.

Data were collected from January 2012 to December 2016, and all patients under 18 years of age with a history of HSP screening during the above period were reviewed. In the HIRA data, patients were identified by a personal identification number as their personal information was not known. It is possible that for some patients in the 2012 records, it was not their initial diagnosis, but they had been previously diagnosed and were being treated again. For that reason, data from 2012 were not included in the study and were used only as a means of identifying previously treated patients, in 2013. Therefore, the study included all patients <18 years of age who were diagnosed with HSP from January 2013 to December 2016 in South Korea. During the period, HSP patients who visited outpatient clinics or emergency rooms and all patients who received hospitalization were surveyed by week, month, season, and year. Data selection and mining were conducted using SAS (version 9.2).

The patients diagnosed with HSP were categorized into the 4 age groups according to the classifications developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development: infant (0–2 years), early childhood (2–5 years), middle childhood (6–11 years), and adolescence (12–18 years).[16]

2.2. Investigation of virus epidemics in South Korea

The Korea Centers for Disease Control and Prevention collect data on pathogens that cause acute respiratory and enteric infectious diseases from various hospitals across the country and publish weekly information on the occurrence of each pathogen in South Korea. We extracted data on viruses causing various respiratory and gastrointestinal diseases from this database. From this data, we identified the patients who tested positive for 8 respiratory viruses (adenovirus, parainfluenza virus, respiratory syncytial virus [RSV], influenza virus, coronavirus, rhinovirus, bocavirus, and metapneumovirus) and 4 enteric viruses (rotavirus, norovirus, enteric adenovirus, and astrovirus) using a viral polymerase chain reaction (PCR) test, from the first week of January 2013 to the last week of December 2016. Epidemic trends were investigated according to the time of onset of the virus by week, month, season, and year.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS 18.0 statistical software (SPSS Inc, Chicago, IL). Differences based on seasons and age groups in the newly diagnosed HSP patients were analyzed using the chi-squared test, and P values $< .05$ were considered statistically significant. To investigate the prevalence of each virus, its trends and seasonality were confirmed using the R program. In general, HSP is known to occur 3 to 10 days after a preceding infection. Usually, a virus that causes an infectious disease is detected a few days after the disease has developed. Therefore, when comparing the time of positive detection of the virus and the time of HSP diagnosis, it is important to use weekly and monthly data. In the correlation analysis, it was confirmed that the P value was <0.05 and the correlation coefficient was >0.5. We used the decomposition of additive time series analysis and correlation analysis to compare the incidence of HSP and the prevalence of each virus.

This study was conducted with approval from the Institutional Review Board (IRB) of the Chung-Ang University Hospital (IRB no. C2016139), and informed consent was waived due to the retrospective nature of the study.

3. Results

3.1. Epidemiology of pediatric HSP patients

From January 2013 to December 2016, 16,940 patients under the age of 18 were diagnosed with HSP in South Korea (Table 1). There were 8126 boys (48.0%) and 8814 girls (52.0%), and the mean age was 7.77 ± 4.73 years. Of all the patients, 980 (5.8%) were infants, 5779 (34.1%) belonged to the early childhood group, 6203 (36.6%) to the middle childhood group, and 3978 (23.5%) were adolescents. Of all the patients, 2983 (17.6%) were hospitalized, and the mean hospital stay was 5.94 ± 3.49 days. The rate of hospitalization was lowest in the summer when 481 (14.9%) of the 3224 diagnosed patients were admitted, while it was highest in autumn when 819 (20.3%) of the 4027 diagnosed patients were admitted to hospitals ($P = .000$). Over 4 years, 15 patients (0.09%) underwent surgical treatments for intussusception or perforation.

Table 1

Epidemiology of pediatric Henoch–Schönlein purpura patients.

Variables	Number of patients (%)
Gender (boys:girls)	8126 (48.0%):8814 (52.0%)
Age at diagnosis, y	7.77 ± 4.73
Infant	980 (5.8%)
Early childhood	5779 (34.1%)
Middle childhood	6203 (36.6%)
Adolescent	3978 (23.5%)
Number of patients per year	
2013	4476 (26.4%)
2014	4284 (25.3%)
2015	3987 (23.5%)
2016	4193 (24.8%)
Number of admitted patients	2983/16,940 (17.6%)
Spring	838/5252 (16.0%)
Summer	481/3224 (14.9%)
Autumn	819/4027 (20.3%)
Winter	845/4437 (19.0%)
Duration of hospital stay, d	5.94 ± 3.49
Number of patients who underwent operation	15 (0.09%)
Total	16,940 (100%)

3.2. Trends and time series of pediatric HSP patients

From 2013 to 2016, the largest number of patients (4476, 26.4%) were diagnosed in 2013. Seasonal analysis of the 4 years showed that while spring had the largest number of patients (5252, 31.0%), summer had the smallest number (3224, 19.0%) (Table 1). The monthly analysis revealed that while the largest number of cases were diagnosed in March (1949, 11.5%), the smallest number was reported in August (959, 5.7%) (Fig. 1). There were no gender differences in the monthly, seasonal, and yearly incidences.

In the analysis based on age groups, the infant, early childhood, and middle childhood groups had the most patients in March (Spring) and least in August (summer) (Table 2). Among the adolescents, most cases of HSP were reported in April (479 patient, 12.0%) and spring (1302 patients, 32.7%). However, unlike in the other age groups, among adolescents, 290 (7.3%), 237 (6.0%), 254 (6.4%), and 269 (6.8%) patients were diagnosed in August through November, respectively. More patients were diagnosed in the summer (985 patients, 24.8%) than in the fall (760 patients, 19.1%).
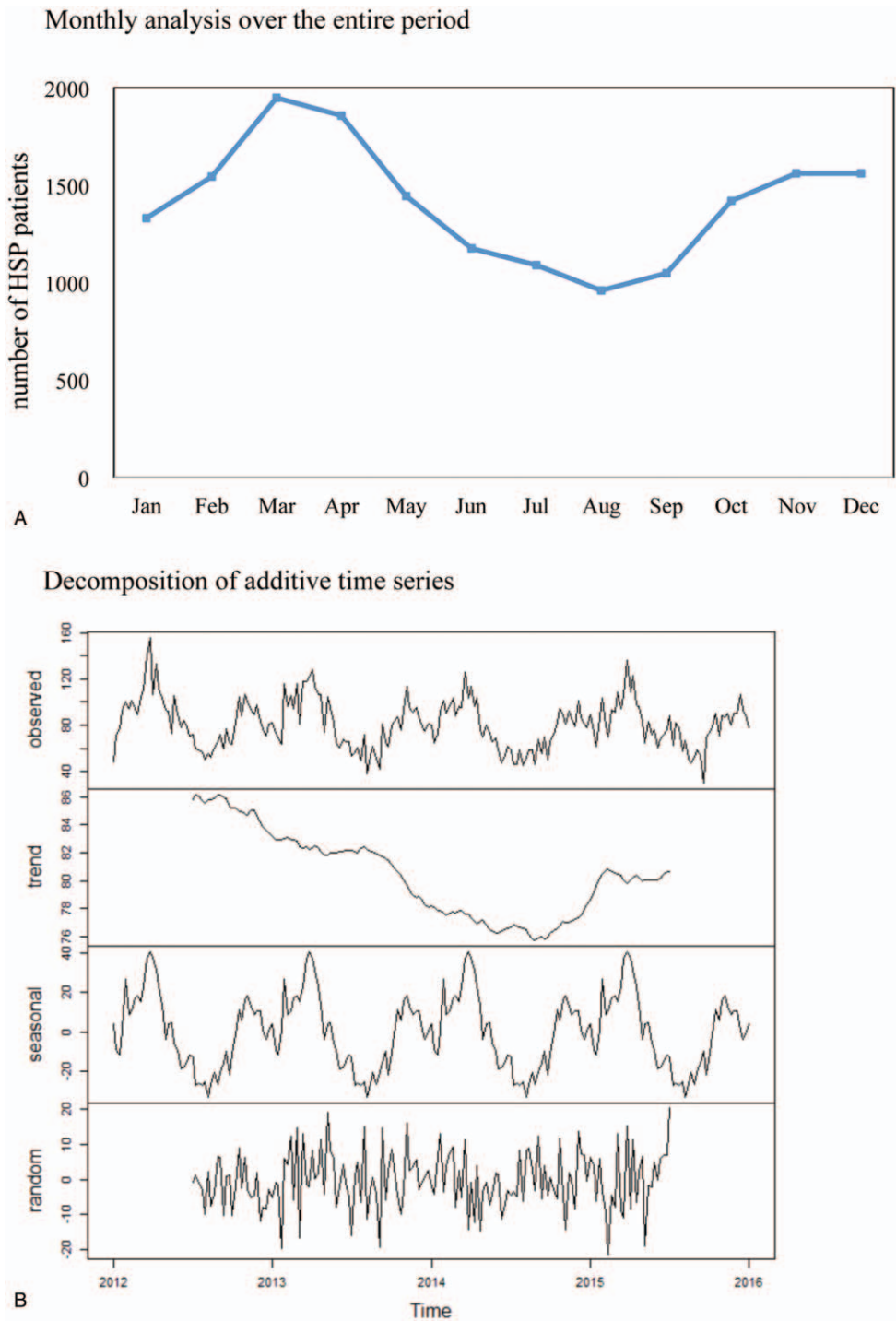

Figure 1. Trends and time series of pediatric Henoch–Schönlein purpura patients.

Table 2

Analysis of monthly, seasonal, and yearly incidences of newly diagnosed Henoch–Schönlein purpura according to age groups.

	Infants (0–2.0 y), n=980 (5.8%)	Early childhood (2.1–6.0 y), n=5779 (34.1%)	Middle childhood (6.1–12.0 y), n=6203 (36.6%)	Adolescence (12.1–18.0 y), n=3978 (25.3%)
Month				
January	78 (8.0%)	492 (8.5%)	457 (7.4%)	305 (7.7%)
February	82 (8.4%)	557 (9.6%)	581 (9.4%)	323 (8.1%)
March	129 (13.2%)	720 (12.5%)	686 (11.1%)	414 (10.4%)
April	100 (10.2%)	601 (10.4%)	678 (10.9%)	479 (12.0%)
May	96 (9.8%)	386 (6.7%)	554 (8.9%)	409 (10.3%)
June	69 (7.0%)	322 (5.6%)	423 (6.8%)	361 (9.1%)
July	82 (8.4%)	302 (5.2%)	372 (6.0%)	334 (8.4%)
August	59 (6.0%)	282 (4.9%)	328 (5.3%)	290 (7.3%)
September	66 (6.7%)	396 (6.9%)	348 (5.6%)	237 (6.0%)
October	78 (8.0%)	578 (10.0%)	509 (8.2%)	254 (6.4%)
November	65 (6.6%)	596 (10.3%)	631 (10.2%)	269 (6.8%)
December	76 (7.8%)	547 (9.5%)	636 (10.3%)	303 (7.6%)
Season				
Spring	325 (33.2%)	1707 (29.5%)	1918 (30.9%)	1302 (32.7%)
Summer	210 (21.4%)	906 (15.7%)	1123 (18.1%)	985 (24.8%)
Autumn	209 (21.3%)	1570 (27.2%)	1488 (24.0%)	760 (19.1%)
Winter	236 (24.1%)	1596 (27.6%)	1674 (27.0%)	931 (23.4%)
Year				
2013	272 (27.8%)	1464 (25.3%)	1576 (25.4%)	1164 (29.3%)
2014	228 (23.3%)	1448 (25.1%)	1535 (24.7%)	1073 (27.0%)
2015	237 (24.2%)	1354 (23.4%)	1500 (24.2%)	896 (22.5%)
2016	243 (24.8%)	1513 (26.2%)	1592 (25.7%)	845 (21.2%)

3.3. Comparison of epidemics of various viruses

Figure 2 shows the monthly, seasonal, and yearly analyses of the patterns of respiratory and gastrointestinal virus epidemics. The positive detection counts for most viruses showed apparent seasonal variations. However, adenovirus appeared to have a fairly uniform pattern throughout the year and did not show any special outbreak. RSV showed a definite tendency from November to January, while the influenza virus was prevalent in winter from January to April. On the contrary, parainfluenza virus showed a tendency in the late spring and early summer such as May or June. The positive detections of coronavirus and rhinovirus were highest from November to January and from October to November, respectively. Rotavirus detection was highest from February to April while detection of norovirus was highest from November to January. However, in the cases of bocavirus, metapneumovirus, enteric adenovirus, and astrovirus, the monthly incidences were low, and it was difficult to identify epidemic patterns. Nevertheless, bocavirus was more prevalent in late spring and early summer than in other seasons and was highest from May to June, while metapneumovirus was more prevalent in April and May.

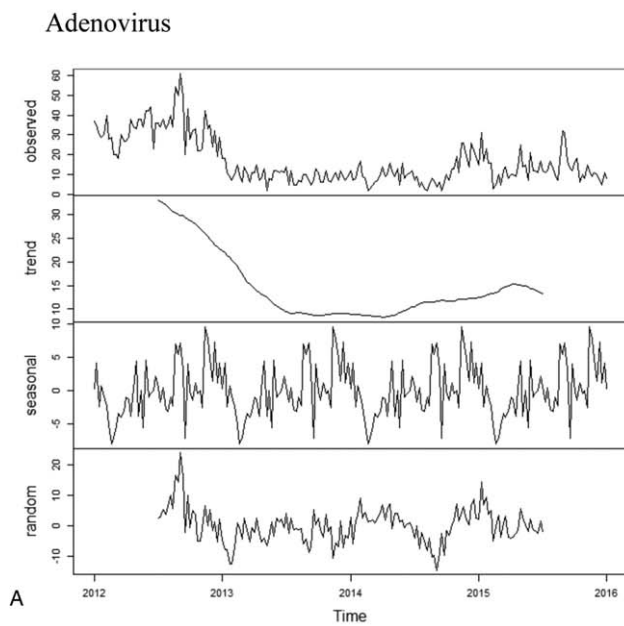### 3.4. Comparative analysis of virus epidemics and HSP

We compared the epidemic patterns of 8 respiratory and 4 enteric viruses with the onset of HSP (Table 3). Since HSP occurs between 3 and 10 days after the preceding infection, the virus epidemics and the occurrence of HSP may appear at similar times in monthly comparisons. Among the 12 viruses, the epidemic patterns of influenza virus and rotavirus were statistically similar to those of HSP.

Table 4 compares the onset of HSP among the different age groups with each of the virus epidemics. No significant correlations were detected in the infant group. In the early childhood group, the onset of HSP was found to be associated with epidemics of RSV, influenza virus, and norovirus. In the middle childhood group, influenza virus and norovirus epidemics were associated with the seasonality of HSP. The epidemic period of bocavirus and rotavirus coincided with that of HSP among the adolescents.
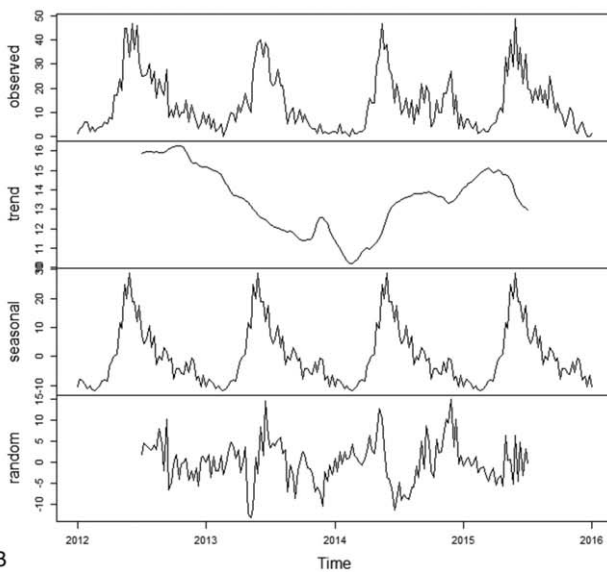
4. Discussion

The relationship between the incidence of HSP and predisposing diseases has been investigated in previous studies. Although various causes have been reported, it is known to occur mainly after respiratory infections such as those caused by streptococci, staphylococci, and mycoplasma.[2,17] There are reports of preceding gastrointestinal tract infections caused by *Helicobacter pylori* or Campylobacter.[5,18,19] Nevertheless, the etiology of HSP often remains unknown. Almost 70% of the cases of HSP in children reported in Spain occurred in fall and winter.[20] This higher incidence in the coldest months further supported an infectious trigger in the pathogenesis of the disease. Moreover, in this population study, upper respiratory infections were described as the potential precipitating event in more than 30% of the cases. By contrast, in the same region of NW Spain, adults in whom HSP occurred in summer were more susceptible to develop permanent renal involvement.[21] However, studies on viral infections as the leading cause of HSP have limitations. HSP was reported in the 2009 influenza virus pandemic, and there have been reports that HSP incidences followed influenza vaccinations.[22–24] However, most of these studies are case studies or cross-sectional studies from several institutions, and no large-scale studies have been conducted using the database of an entire country's healthcare system. In addition, different types of viral infections prevail in different regions, and their timings could vary. For this reason, our findings are important and meaningful because this is the first study to investigate the relationship between HSP and the preceding infectious diseases
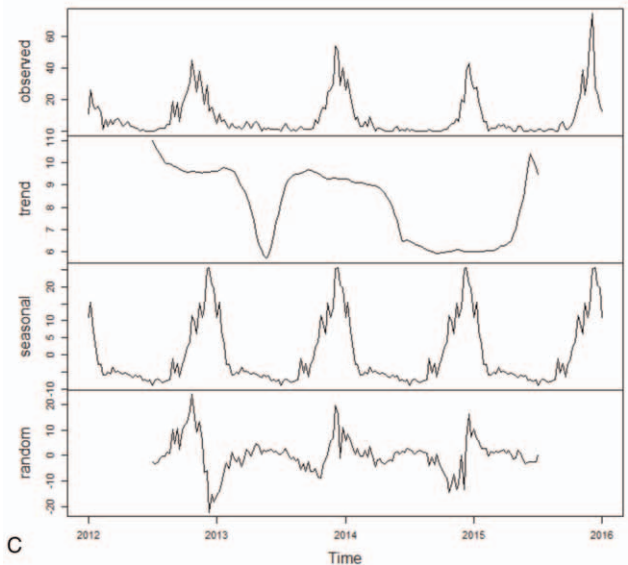
Adenovirus

A

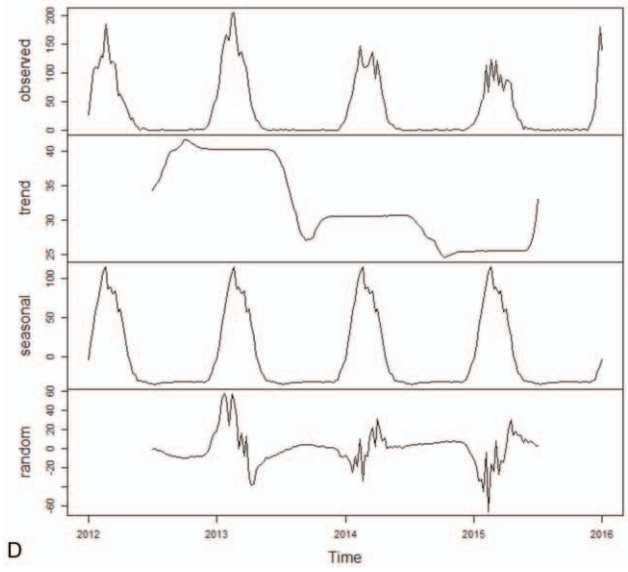## Parainfluenzavirus

B

Figure 2. Decomposition of additive time series of acute respiratory and enteric viruses.

Respiratory syncytial virus
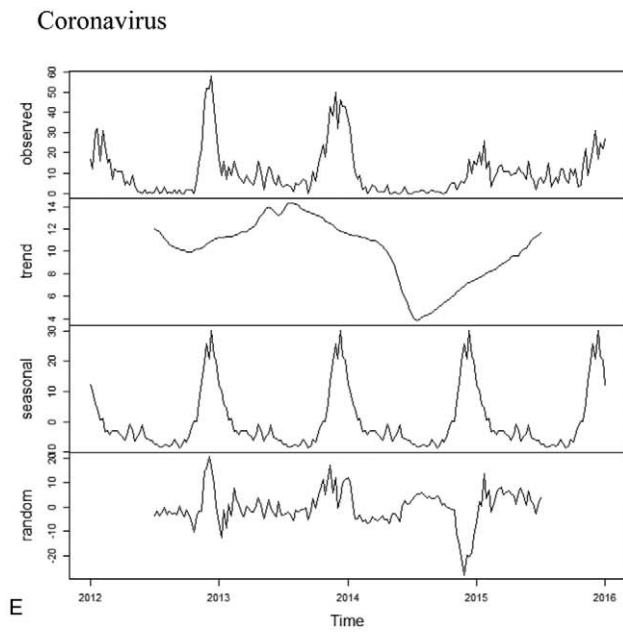

C

Influenza virus

D

Figure 2. (Continued).

using the national health data from the HIRA and the Korea Centers for Disease Control and Prevention databases. First, through our investigation, we were able to identify the epidemiology of HSP and compare it with previous reports. Though HSP was known to affect boys predominantly, in our study, it was found to occur more in girls in South Korea.[2,6,25] Previous studies have reported that HSP is commonly seen in winter or from late autumn to early spring, and we have confirmed a similar pattern.[2,6,26] We found that it predominantly occurred in spring and specifically in March, and less in the summer particularly in August, although the number of cases reported in August was never <5.7% of that reported for the whole year.
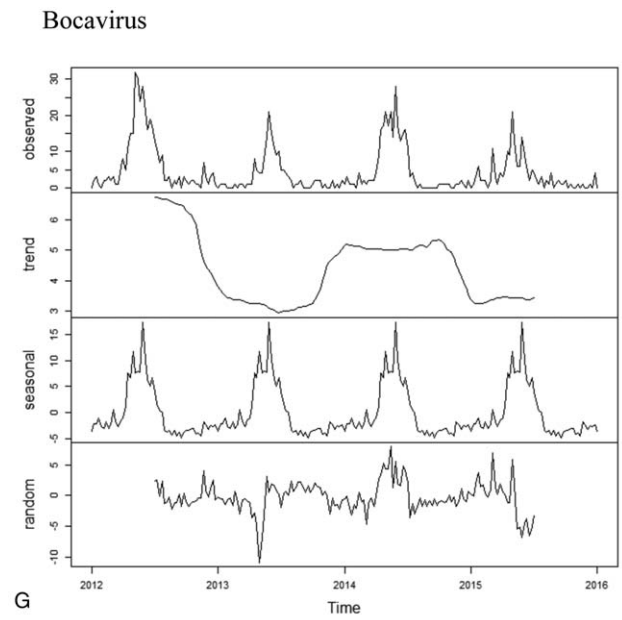
Of all the HSP patients in this study, 17.6% were hospitalized, and 15 of them were operated on. However, since only the

patients who were first diagnosed with HSP between January 2013 and December 2016 were included in the study, we could only identify those who were hospitalized at the time of the first diagnosis. Patients who visited the hospital for the first time and did not get hospitalized, but were later admitted or operated due to severe symptoms, were excluded from the study. Therefore, the proportion of the inpatients and the number of surgical patients are expected to be slightly higher than found in our results
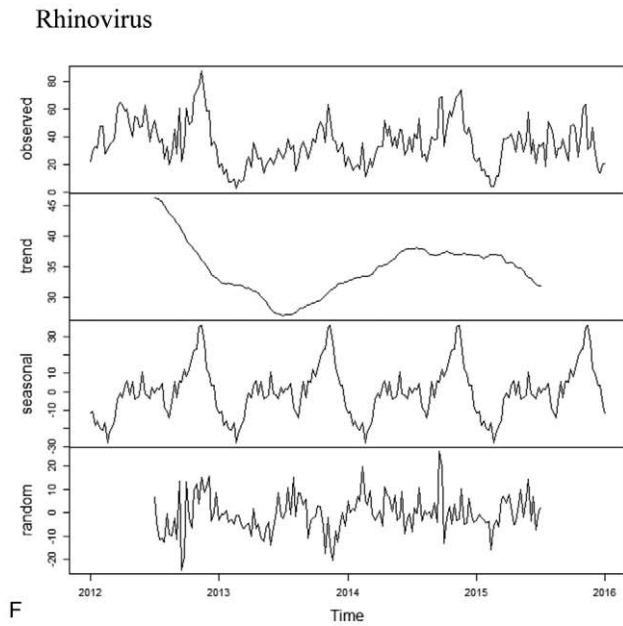
Based on our results, some of the known infectious causes of HSP were identified. Previously known infectious agents, such as adenovirus, were associated with HSP and were found to be statistically significant even in our study using national health data.[2,26] However, adenovirus did not show any significant seasonal tendency and was found to occur evenly throughout the year. Several studies have described the influenza virus to be a
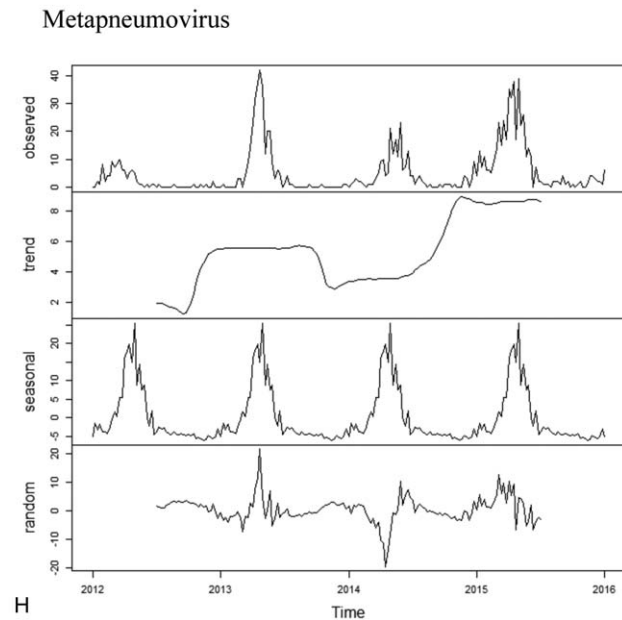
Figure 2. (Continued).

Figure 2. (Continued).

predisposing cause of HSP with significant association with HSP incidences and we confirmed similar result.[22–24] On the other hand, we also confirmed a possibility of rotavirus that it has not been previously reported as predisposing cause of HSP. However, we cannot conclude that the incidence of HSP is triggered by only 1 causative virus.

Interestingly, unlike the other age groups, the adolescence group showed more HSP patients in summer (August) than during autumn (September to November). Due to the number of patients in this group, it is expected that the overall outbreak of HSP among patients in August was more, though a clear cause for this increase in incidence could not be determined. However, our finding with bocavirus, which appeared to be most active during relatively warm weather, is clearly interesting. Although not investigated in this study, additional studies are needed to

determine the association with enteroviruses that occur in summer. Comparison of the virus epidemics based on the age groups of the patients also produced interesting results. Depending on the age group, there were various types of viruses that were temporally associated with HSP. RSV showed a similar temporal pattern in the early childhood group but was not confirmed in all patients and other age groups. While norovirus was associated with HSP in early childhood and middle childhood group, rotavirus that rarely occurred in early adolescence also showed an association with HSP. Even if it occurs after a viral infection, it is difficult to confirm that a single virus is a causative agent. Nevertheless, our study is significant because it suggests the possibility of a causative disease by confirming the coincidence of HSP and some viruses that were not previously linked to HSP such as rotavirus, norovirus, or bocavirus. Further studies are
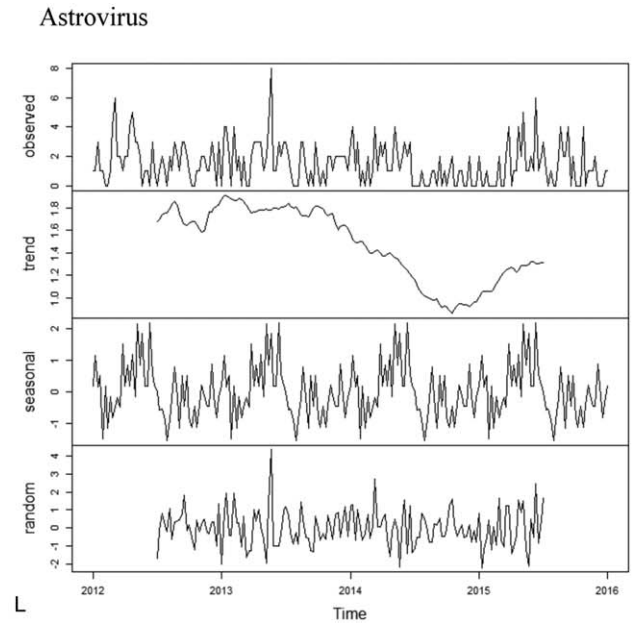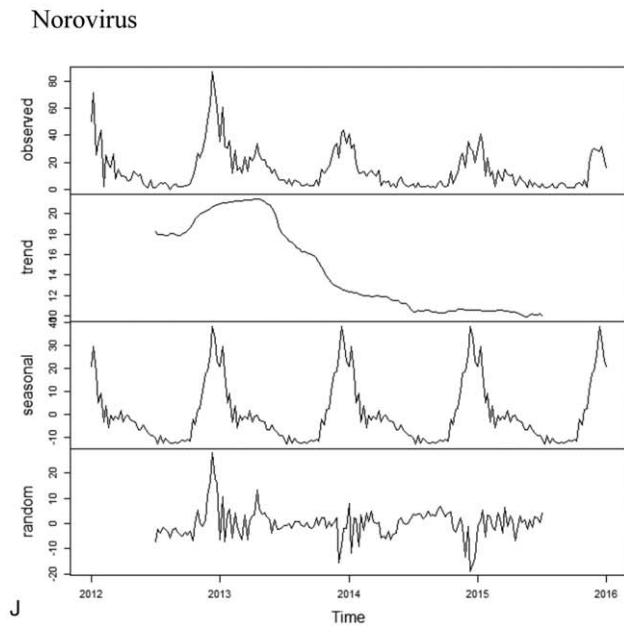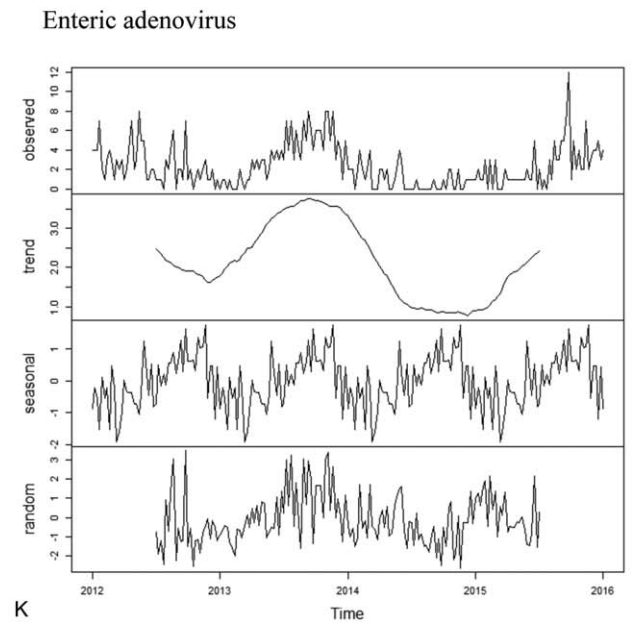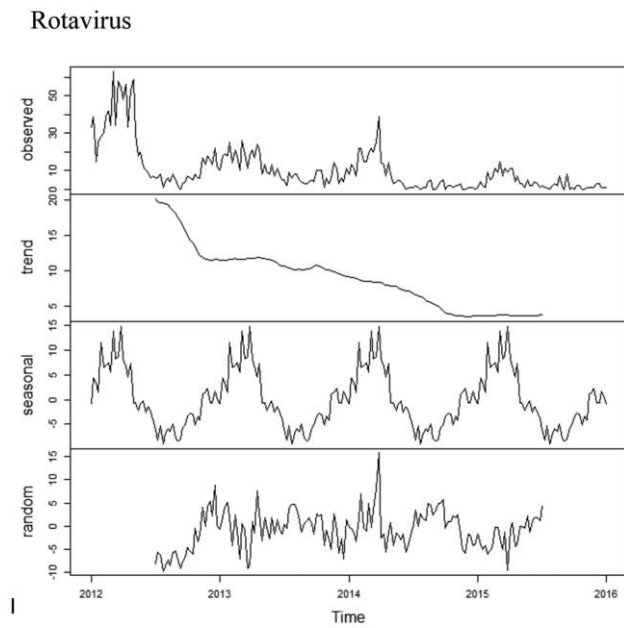
Rotavirus

Enteric adenovirus

Norovirus

Figure 2. (Continued).

Astrovirus

Figure 2. (Continued).

needed to confirm our findings. Because existing predisposing factors are often not directly evidenced by causal relationships, but rather through anecdotal cases, the results of this study about relationship to seasonal variation may raise the possibility of a novel pathogen associated with HSP.

However, our study has some limitations. First, we compared the timings when a particular virus was positively identified and the incidence of HSP. The results were confirmed using statistical methods by experts specializing in preventive medicine and statistics. But it was not possible to confirm whether the virus caused HSP. It is known that IgA-containing immune complexes triggered by infectious diseases are deposited on organs such as skin, kidneys, and gastrointestinal tract and can cause HSP, and we can only assume that the viruses suspected of causing HSP have similar mechanisms.[2,27,28] However, studies on whether only specific viruses or bacteria cause HSP should be continued. Second, there is a limitation in the extent of virus detection. While the data included HSP outbreaks for all patients <18 years of age in South Korea, virus detection tests were given to only patients with severe respiratory symptoms. Therefore, the patients who were not tested but have symptoms were not included in the study. Also, if the causative virus itself is not as severe as rhinovirus, its detection rate would have been much lower than actual incidence. On the contrary, if there was, for example, an influenza virus epidemic which caused severe symptoms, and relatively more tests were conducted, its actual detection rate would have been higher than that of other viruses. Finally, there is a limitation in the HIRA data. The possibility of duplicate diagnoses could not be totally excluded, even though only the initial diagnosis was included by examining the cases by the

Table 3

Correlation analysis between Henoch–Schönlein purpura occurrence and prevalence of viral infections.

	Number of positive detection	*P*	Correlation coefficient
Adenovirus	3478	.891	0.009
Respiratory syncytial virus	2830	.022	0.159
Parainfluenza virus	1842	.000	−0.335
Influenza virus[*]	7167	**.000**	**0.520**
Corona virus	2184	.005	0.194
Rhinovirus	7472	.216	0.086
Bocavirus	946	.555	−0.041
Metapneumovirus	1048	.000	0.300
Rotavirus[*]	2163	**.000**	**0.525**
Norovirus	2973	.000	0.246
Enteric adenovirus	492	.192	−0.091
Astrovirus	312	.327	0.068

Table 4

Correlation analysis between Henoch–Schönlein purpura occurrence and prevalence of viral infections according to age groups.

	Infant		Early childhood		Middle childhood		Adolescent	
	P	γ	*P*	γ	*P*	γ	*P*	γ
Adenovirus	.445	0.113	.908	0.017	.823	0.033	.138	0.217
RSV	.962	0.007	**.000**	**0.621**	.002	0.428	.426	−0.118
Parainfluenza virus	.486	−0.103	.000	−0.653	.001	−0.446	.188	0.193
Influenza virus	.002	0.439	**.000**	**0.519**	**.000**	**0.638**	.007	0.386
Coronavirus	.629	0.071	.000	0.492	.001	0.462	.579	−0.082
Rhinovirus	.855	0.027	.751	0.047	.736	0.050	.752	−0.047
Bocavirus	.010	0.369	.137	−0.218	.687	0.060	**.000**	**0.537**
Metapneumovirus	.001	0.458	.362	0.135	.013	0.358	.008	0.378
Rotavirus	.001	0.450	.006	0.390	.001	0.450	**.000**	**0.630**
Norovirus	.389	0.127	**.000**	**0.565**	**.000**	**0.582**	.274	0.161
Enteric adenovirus	.817	−0.034	.527	0.094	.729	−0.051	.884	−0.022
Astrovirus	.056	0.277	.803	−0.037	.501	0.100	.005	0.399

Significant findings at $P < .05$.
γ = correlation coefficient, RSV = respiratory syncytial virus.

unique number given to each individual. Also, for the same reason, patients who visited clinics for recurrence and not for a simple follow-up, would not be identified. Because the patients evaluated were based on the HIRA data, information regarding their clinical aspects was not included in this study. It is necessary to investigate whether the clinical features differ based on the infectious agent causing HSP, and information about the prognosis should also be evaluated. In addition, the diagnosis of HSP was based on the final diagnosis only, not grounded on all patients or chart review, so there may be some errors in the total number of patients. Nevertheless, our study will be the first to investigate an association between the occurrence of HSP and outbreaks of different viruses using the National health data.

In conclusion, we have confirmed that the occurrence of pediatric HSP in Korea shows a seasonal tendency, which is age-dependent and related to the exposure of infectious agents, and suggest that some respiratory or enteric viruses may play an important role in pathophysiology. It is necessary to confirm the exact causal relationships through further long-term epidemiological studies.

Author contributions

Hyun Ho Hwang and Dae Yong Yi: designed the study and wrote the manuscript.
Hyun Ho Hwang: analyzed the data (The Korea Centers for Disease Control and Prevention).
Byung-Sun Choi and Dae Yong Yi: investigated and analyzed the data (HIRA).
In Seok Lim: critically reviewed the manuscript.
Data curation: Hyun Ho Hwang.
Formal analysis: Dae Yong Yi.
Supervision: In Seok Lim.
Validation: Byung-Sun Choi.
Writing – original draft: Hyun Ho Hwang, Dae Yong Yi.
Writing – review & editing: In Seok Lim.

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