



The occurrence of infection-related systemic diseases in Korean children and adolescents has decreased after the spread of the COVID-19 pandemic: a multicenter retrospective study

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Background: The occurrences of infection-related systematic diseases, such as Henoch-Schönlein Purpura (HSP), intussusception, and mucocutaneous lymph node syndrome (MCLS) may have decreased, similarly to the decreased occurrence of infectious diseases following the Coronavirus disease 2019 (COVID-19) pandemic. We aimed to investigate whether there was a change in the occurrence of these diseases in South Korea after the spread of the COVID-19 pandemic.

Methods: In this multicenter, retrospective study conducted in 16 medical centers in South Korea

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patients diagnosed with HSP, intussusception, and MCLS at the age of <18 years between January 2016 and December 2020 were included. New occurrences of these three diseases were investigated monthly and annually, while to compare between the pre- and post-COVID-19 era cases, new occurrences between 2017–2019 and 2020 were compared. Additionally, the total annual occurrence rate was calculated by dividing each center's occurrence into the annual population per 100,000 of the population <18 years in each region that the center covers.

Results: A total 6,857 patients were included in this study. From 2017 to 2020, the number of patients diagnosed with HSP, intussusception, MCLS at the age of <18 years were 1,301, 1,693, and 3,863 patients, respectively. The average number of patients during the three years before the COVID-19 pandemic were each 379.7, 505.3, and 1,112.0 for HSP, intussusception, MCLS, respectively, which each decreased by 57.3%, 65.0%, 52.6% to 162, 177, 527 in 2020, respectively. Furthermore, the total annual occurrence rate showed a significant decrease in 2020 compared to 2017 to 2019 in all three diseases (2017–2020; HSP: 11.85, 12.96, 10.52, and 5.48; intussusception: 13.94, 16.97, 16.31, and 5.98; MCLS: 33.89, 35.11, 34.69, and 17.82, respectively).

Conclusions: We revealed that the occurrence of HSP, intussusception, and MCLS, which are representative of infection-related systemic diseases in the pediatric population, decreased significantly after the spread of the COVID-19 pandemic.

Keywords: COVID-19; Henoch-Schönlein Purpura; intussusception; mucocutaneous lymph node syndrome

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Introduction

It is likely that the year 2020 will be recorded on the pages of human history as a drastic year. Due to the Coronavirus disease 2019 (COVID-19) global pandemic, the daily lives of ordinary people were forced to change in many ways. This change was more direct in the healthcare sector, where they had no choice but to face the disease directly. Medical staff encountered many patients diagnosed with COVID-19, vaccines were developed for prevention, and efforts were made to cure infected patients. In addition to this direct impact of the COVID-19 infection, numerous medical staff and researchers worldwide conducted many studies related to the pandemic (1-3), such as research on its relationships with underlying diseases, treatment, prognosis, and most recently, vaccination.

However, other medical issues exist that are indirectly associated with the COVID-19 pandemic. Among these issues are the public awareness of the infection and increased enlightenment on the importance of personal hygiene, which is now demonstrated in everyday practice by social distancing, wearing masks, and washing hands (4). These new behaviors have decreased the development of various infectious diseases other than COVID-19 infections.

Furthermore, visits to medical institutions have decreased, which has also resulted in reduced medical costs (5-7). This tendency is also expected in South Korea, where the COVID-19 epidemic began early compared to other countries (8).

At this point, we were curious whether this reduced change in the occurrence of infectious diseases influenced by the COVID-19 pandemic was limited only to respiratory or gastrointestinal viral diseases. Based on literature, infection-related systematic diseases, such as Henoch-Schönlein Purpura (HSP), intussusception, and mucocutaneous lymph node syndrome (MCLS), are more likely to occur in children and adolescents than adults (9-11). HSP is generally known to occur in 10–30 patients per 100,000 under the age of 18, and data from South Korea showed that HSP had occurred in approximately 17,000 patients from 2013 to 2016 (9,12). Meanwhile, intussusception has been reported to occur in 9–328 per 100,000, and approximately 25,000 patients have been reported in South Korea from 2008 to 2016 (10,13). In the case of MCLS, there are regional differences in incidence, and the incidence in South Korea is approximately 217 per 100,000 population (14).

While limitations in explaining the direct causal

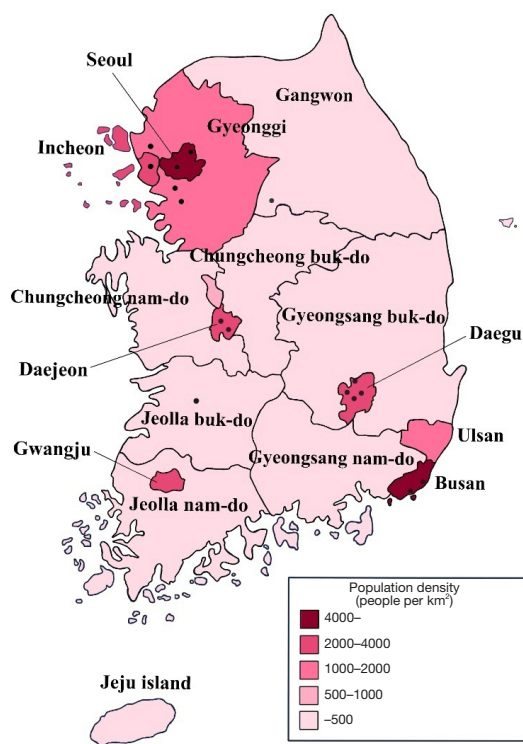


Figure 1 Geographic location of the participating centers on the map of South Korea.

relationship between these diseases and infections were observed, their associations with some pathogens have also been elucidated (15,16). Currently, limited published data exist regarding the changes in the occurrence of these infection-related systematic diseases in the post-COVID-19 era. Therefore, in this study, we aimed to investigate whether there was a change in the occurrence of infection-related diseases, such as HSP, intussusception, and MCLS, in South Korea during the COVID-19 pandemic.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tp-21-315>).

Methods

Patient selection

This study was a multicenter, retrospective study conducted in 16 medical centers in South Korea (Figure 1). Patients included were those diagnosed with HSP (ICD 10 code: D690.02), intussusception (K561), and MCLS (M303) at the age of <18 years between January 2016 and December

2020. All participating centers were tertiary hospitals serving as referral centers in each region who also provided medical care for direct visits without referrals. Furthermore, medical charts were reviewed, and those whose diagnosis was indefinite were excluded. Additionally, patients who had previously been diagnosed with the same disease before the study period were also excluded. For this reason, data from 2016 were excluded, whereas, only data from January 2017 to December 2020 were included. New occurrences of these three diseases at the participating centers were investigated monthly and annually, while to compare between the pre- and post-COVID-19 era cases, new occurrences between 2017–2019 and 2020 were compared.

The rate of change was determined based on the first year to calculate changes in the number of patients each year for each disease. We also identified the average number of patients over the 3 years from 2017 to 2019, and the rate of change in 2020. The rate of changing patients' numbers was then calculated using the following equation:

$$\text{The rate of change (\%)} = \frac{(\text{patient number of target year} - \text{patient number of the reference year})}{\text{patient number of reference year}} \times 100 \quad [1]$$

Additionally, to identify the annual occurrence rate of these three diseases in each region, the population of people <18 years were applied using population census data obtained from Statistics Korea, which is a government organization for statistics under the Ministry of Economy and Finance (Table S1). Then, the total annual occurrence rate was calculated by dividing each center's occurrence into the annual population per 100,000 of the population <18 years in each region that the center covers. Thereafter, we summed the annual occurrence rate of each center.

Statistical analysis

To compare the fluctuations of the total annual occurrence rates over the years, a 95% confidence interval was calculated using the Clopper-Pearson method (17). Logistic regression analysis was performed to investigate the odds ratio (OR) for each year with 2020 as the reference. Data were considered statistically significantly different when the P value was <0.05. Statistical analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The study was conducted in accordance with the

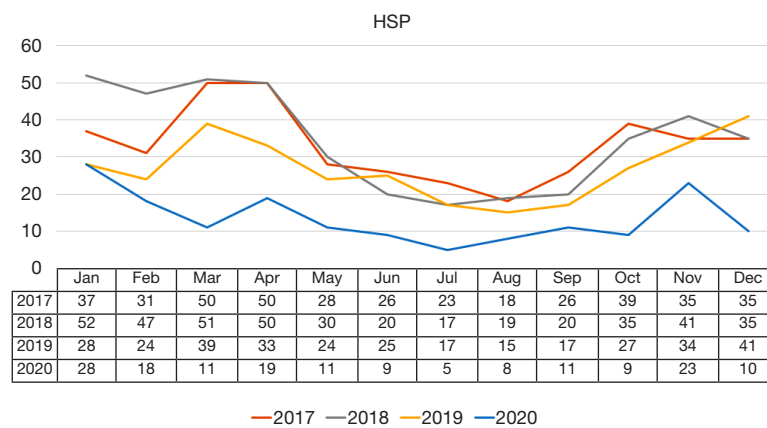


Figure 2 The occurrence of HSP before and after the spread of the COVID-19 pandemic. HSP, Henoch-Schönlein Purpura; COVID-19, Coronavirus disease 2019.

Declaration of Helsinki (as revised in 2013). The study was conducted with approval by the Institutional Review Board of 16 participating institutions including that of Chung-Ang University Hospital (IRB No.: 2012-020-19344) and individual consent for this retrospective analysis was waived.

Results

Number of included patients

A total of 6,857 patients were included in this study. From 2017 to 2020, the number of patients diagnosed with HSP, intussusception, MCLS at the age of <18 years in the participating centers were 1,301, 1,693, and 3,863 patients, respectively.

Changes in the occurrence of HSP

The number of patients diagnosed with HSP at the age of <18 years for the four years from 2017 to 2020 was 398, 417, 324, and 162, respectively (Figure 2). The average number of patients during the three years before the COVID-19 pandemic was 379.7, which decreased by 57.3% to 162 in 2020. When comparing the monthly occurrence patterns between each year, the occurrence of HSP in each month decreased significantly in 2020 compared to the previous three years except in January, which was before the COVID-19 endemic started to spread in South Korea.

Furthermore, according to the Clopper-Pearson method, the total annual occurrence rates from 2017 to

2020 was 11.85 (95% CI: 10.72–13.08), 12.96 (95% CI: 11.74–14.26), 10.52 (95% CI: 9.41–11.73), and 5.48 (95% CI: 4.67–6.39) per 100,000 population, respectively (Figure 3). Logistic regression analysis revealed that the odds ratios of the total annual occurrence rate were each significantly higher in 2017–2019 compared to 2020, respectively (all P<0.001) (Table 1).

Changes in the occurrence of intussusception

The number of patients diagnosed with intussusception at the age of <18 years for the four years from 2017 to 2020 was 468, 546, 502, and 177, respectively (Figure 4). The average number of patients during the three years before the COVID-19 pandemic was 505.3, which decreased by 65.0% to 177 in 2020. Furthermore, comparing the monthly occurrence of patterns between each year showed results similar to that of HSP. The occurrence of intussusception during each month also decreased significantly in 2020 compared to the previous three years except in January, which was before the COVID-19 endemic started to spread in South Korea.

Similarly, according to the Clopper-Pearson method, the total annual occurrence rates from 2017 to 2020 was 13.94 (95% CI: 12.70–15.26), 16.97 (95% CI: 15.57–18.45), 16.31 (95% CI: 14.91–17.80), and 5.98 (95% CI: 5.14–6.93) per 100,000 population, respectively (Figure 3). Logistic regression analysis revealed that the odds ratios of the total annual occurrence rate were each significantly higher in 2017–2019 compared to 2020, respectively (all P<0.001) (Table 1).

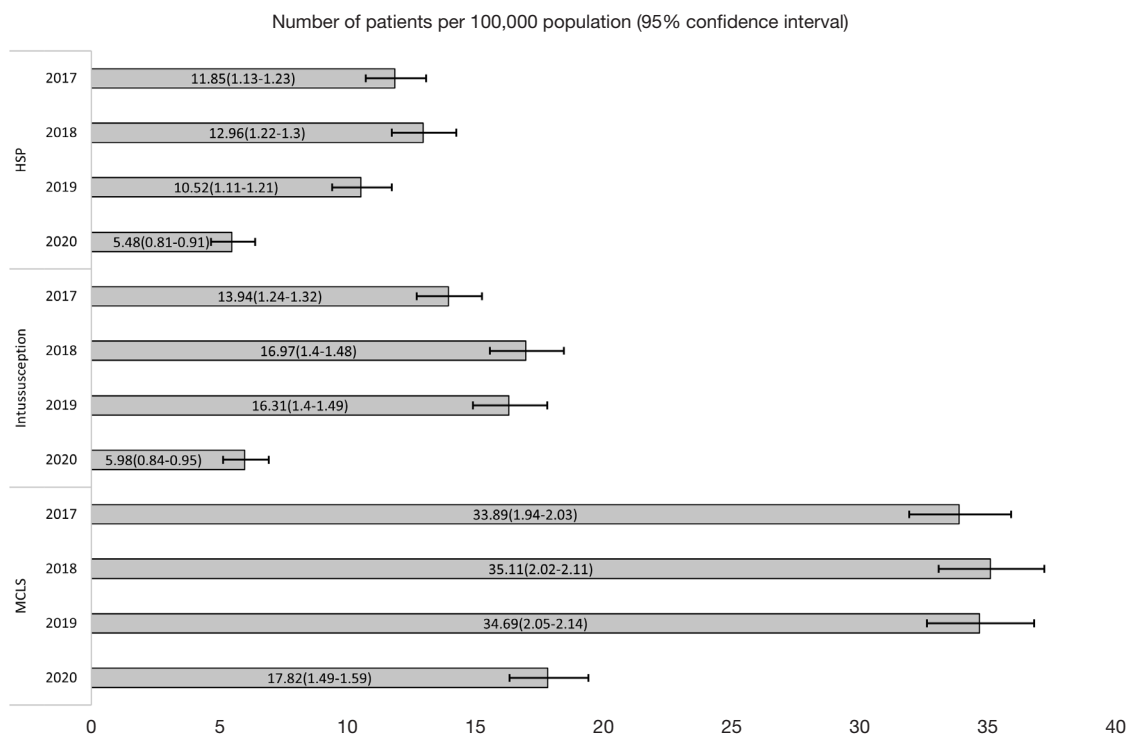


Figure 3 The total annual occurrence rate before and after the spread of the COVID-19 pandemic. COVID-19, Coronavirus disease 2019; HSP, Henoch-Schönlein Purpura; MCLS, mucocutaneous lymph node syndrome.

Table 1 Logistic regression analysis of each disease according to the occurrence rates by year

Disease	Year	OR (95% CI)	P
HSP	2017	2.16 (1.80–2.60)	<0.001
	2018	2.37 (1.97–2.84)	<0.001
	2019	1.92 (1.59–2.32)	<0.001
	2020	Reference	
Intussusception	2017	2.33 (1.96–2.77)	<0.001
	2018	2.83 (2.40–3.36)	<0.001
	2019	2.72 (2.30–3.23)	<0.001
	2020	Reference	
MCLS	2017	1.90 (1.72–2.11)	<0.001
	2018	1.97 (1.78–2.19)	<0.001
	2019	1.95 (1.75–2.16)	<0.001
	2020	Reference	

HSP, Henoch-Schönlein Purpura; MCLS, mucocutaneous lymph node syndrome; OR, odds ratio; CI, confidence interval.

Changes in the occurrence of mucocutaneous lymph node syndrome

The number of patients diagnosed with MCLS at the age of <18 years for the four years from 2017 to 2020 was 1,138, 1,130, 1,068, and 527, respectively (*Figure 5*). Furthermore, the average number of patients during the three years before the COVID-19 pandemic began was 1,112.0, which decreased by 52.6% to 527 in 2020. Comparing the monthly occurrence patterns between each year showed results similar to that of HSP and intussusception. The occurrence of MCLS in each month decreased significantly in 2020 compared to the previous three years except in January and February, which was before the COVID-19 endemic started to spread in South Korea.

According to the Clopper-Pearson method, the total annual occurrence rates from 2017 to 2020 was 33.89 (95% CI: 31.95–35.92), 35.11 (95% CI: 33.09–37.22), 34.69 (95% CI: 32.64–36.83), and 17.82 (95% CI: 16.33–19.41) per 100,000 population, respectively (*Figure 3*). Logistic regression analysis revealed that the odds ratios of the total

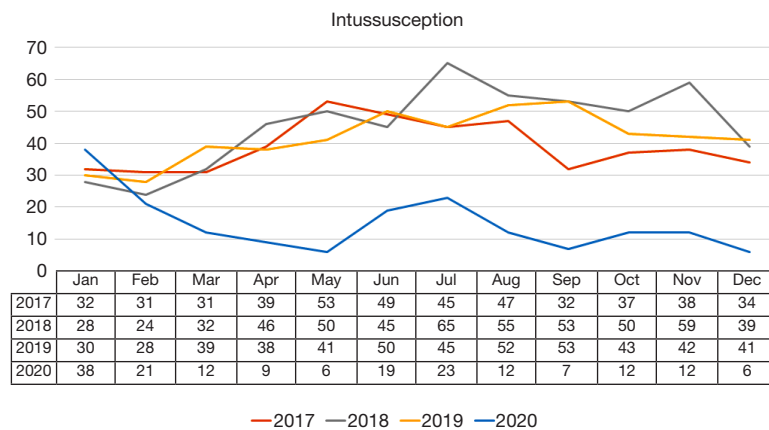


Figure 4 The occurrence of intussusception before and after the spread of the COVID-19 pandemic. COVID-19, Coronavirus disease 2019.

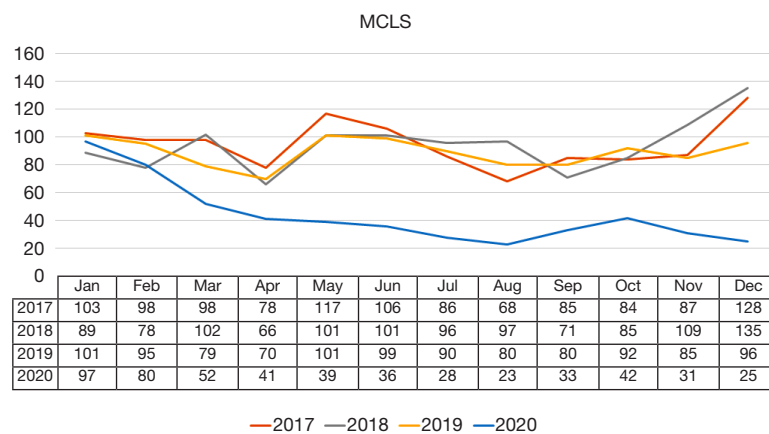


Figure 5 The occurrence of MCLS before and after the spread of the COVID-19 pandemic. MCLS, mucocutaneous lymph node syndrome; COVID-19, Coronavirus disease 2019.

annual occurrence rate were each significantly higher in 2017–2019 compared to 2020, respectively (all $P < 0.001$) (Table 1).

Discussion

This study is the first to identify the changes in occurrence patterns of infection-related systematic diseases in children and adolescents following the COVID-19 pandemic.

Through this nationwide study, we have identified that after the spread of the COVID-19 pandemic, the occurrence of infection-related systematic diseases, such as HSP, intussusception, and MCLS decreased by more than half compared to before. Furthermore, this pattern changes in infection-related systematic diseases, which reduced along with a decrease in infectious diseases,

provide indirect evidence that the occurrences of these diseases were associated with a preceding infection. It has been elucidated in previous studies as well that these infection-related systematic diseases occurred during a particular season (9,10,18–20). Therefore, although limitations still exist in explaining the direct causality or mechanisms, the associations between mycoplasma or influenza virus in HSP, adenovirus in intussusception, and a preceding respiratory illness in MCLS are well-known (14–16,21).

In South Korea, a rapid increase in the incidence of COVID-19 infections was observed in Daegu and North Gyeongsang Province between February and March 2020 when the pandemic had not yet spread to most Western countries. The second and third pandemic spread was also observed in summer and late 2020 in the densely populated

Seoul and Gyeonggi Province. According to this study, we identified that regardless of the regional differences in COVID-19 incidence, the occurrence of these three diseases over the past year experienced a sharp decrease since February 2020. However, this decrease was indirectly related to the decrease in other infectious diseases following the COVID-19 pandemic, but is probably due to the increased awareness of COVID-19, thereby leading to the spread of strict personal hygiene management all over the country since early 2020. Similar patterns of this phenomenon were observed as well in the decreased occurrence of other diseases, including the decrease in hospital visits (8,22).

Of course, there is a possibility that patients refrained from visiting hospitals despite symptoms that had occurred. A possibility exists also that treating other diseases at centers was difficult due to the COVID-19 pandemic. However, when considering the low medical fee and easy accessibility to medical institutions in South Korea, including the fact that most of the participating centers were not dedicated COVID-19 hospitals, it is unlikely that visits to these centers would have decreased for the aforementioned reasons. Moreover, considering the emergent medical condition of intussusception, ongoing associated long-term fever and various symptoms of MCLS, including purpura and complications in HSP, there is no doubt that the patient would have visited a medical institution (23).

Therefore, the reason why we considered these three diseases for the investigation was that these diseases show clear seasonality, and misdiagnosis seldomly occurs in tertiary medical settings. Our investigation of course cannot represent all patients in South Korea. However, all the centers that participated in the study were representative tertiary referral hospitals in each region, and limitations in treating these infection-related systematic diseases at primary medical institutions have been observed. Hence, it is likely that most of the patients with these diseases who resided within the region that the participating centers covered, would have visited that center. Therefore, the investigated data from each participating center are likely to have represented the incidence of infection-related systematic diseases in the region that center covers.

Furthermore, this study has some value as we compared only the changes in the number of cases; 3 years prior and 1 year after the start of the pandemic at the same centers, which are representative tertiary centers of the region.

Moreover, to minimize bias related to the change in the population, we applied the population number of residents under 18 years in the region and identified the occurrence rate. Finally, despite the dramatic decrease of infectious diseases over the past year, the relatively low decrease in the occurrence of these three diseases compared to infectious diseases implicated that the cause of these three diseases was not merely due to preceding infections.

Although, the occurrence of MCLS had decreased after the COVID-19 outbreak in South Korea according to the present study, there have been increasing reports of a Kawasaki disease-like, multisystem inflammatory syndrome in children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3,24). This has been termed “Paediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS)”, in the UK, or “Multisystem Inflammatory Syndrome in Children (MIS-C) associated with Coronavirus Disease 2019 (COVID-19)”, in the US, although debate is still ongoing regarding the temporal association and nature of these hyper-inflammatory syndromes. Although no case of MIS-C associated with COVID-19 was reported in the present study, further investigations are required in this field as the COVID-19 pandemic continues. Moreover, because SARS-CoV-2 itself is a virus, there is a possibility of occurrence of infection-related systematic diseases after infection with SARS-CoV-2. A case of HSP has been reported after infection with SARS-CoV-2 (25).

This study has some limitations. First, as mentioned previously, this study did not include all the hospitals in South Korea. Therefore, it is hard to represent the general population of the country. Second, due to the retrospective nature of this study, some patients with the actual disease may have been excluded because of a misdiagnosis. Third, despite the fact that we not only analyzed the diagnostic codes but also investigated the electronic medical records of each patient, we may have missed some patients during this process. Therefore, caution is required when interpreting the results of this study. Future nationwide studies may better elucidate the changes in incidence of infection-related systemic diseases in the post-COVID-19 era.

In conclusion, we revealed that the occurrence of HSP, intussusception, and MCLS, which are representative of infection-related systemic diseases in the pediatric population, decreased significantly after the spread of the COVID-19 pandemic. These results also provide indirect evidence of their association with preceding infections.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was conducted with approval by the Institutional Review Board of 16 participating institutions including that of Chung-Ang University Hospital (IRB No.: 2012-020-19344) and individual consent for this retrospective analysis was waived.

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