DOI: 10.1002/jmv.26435

COMMENTARY

JOURNAL OF MEDICAL VIROLOGY WILEY

No temporal association between human coronavirus and Kawasaki disease: National data from South Korea

Seung-Ah Choe[1] | Hyo Soon An[2] | Young June Choe[3]

[1]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

[2]Department of Pediatrics, Seoul National University Hospital, Seoul, Korea

[3]Department of Social and Preventive Medicine, Hallym University, Chuncheon, Gangwon-do, Korea

Correspondence
Young June Choe, MD, PhD, Assistant Prof, Department of Social and Preventive Medicine, Hallym University College of Medicine, 1, Hallymdaehak-gil, Chuncheon-si, Gangwon-do 24252, Republic of Korea.
Email: ychoe@hallym.ac.kr

Keywords
coronavirus, epidemiology, seasonal incidence

Funding information
Hallym University Research Fund, Grant/Award Number: HRF-201912-009

Despite advances in our understanding of the pathogenesis of Kawasaki disease, its association with respiratory viruses remains unclear. Previous studies have suggested a possible association between human coronavirus (HCoV) NL63 and 229E with Kawasaki disease, however none were confirmed to be causal.[1,2] Amid coronavirus disease 2019 (COVID-19) pandemic and its hypothesized association with Kawasaki-like illness,[3] it is important to understand the temporal association between Kawasaki disease and the HCoVs. With one of the highest incidence rate of Kawasaki disease, the large sample size data from South Korea, would provide opportunity to investigate the possible association between HCoVs and Kawasaki disease.[4]

We used national representable data on respiratory virus activity from the Korea Influenza and Respiratory Viruses Surveillance System (KINRESS), the sentinel surveillance in operation since 2009, to extract monthly occurrence of HCoV.[5] The KINRESS collects respiratory specimens from patients with acute respiratory illness visiting 52 medical facilities across the country. HCoVs are tested using reverse transcription-polymerase chain reaction. We calculated the mean monthly proportion of HCoV to assess the relative prevalence among all respiratory specimens. We accessed the Health Insurance Review and Assessment Service database, a single-payer that covers more than 99% of the residents. The monthly number of patients diagnosed with Kawasaki disease, coded with ICD-10-CM with M303, was retrieved from January 2016 to October 2019. The monthly new incident of Kawasaki disease was merged with the monthly proportion of HCoV. Linear regression analysis was done to assess differences in the log-transformed incidence of Kawasaki disease across season and year, and time series were plotted using distributed lag linear models (DLNMs).[6] We estimated the overall cumulative effect of a 10-unit increase in the proportion of HCoV infection over 1 month of lag on the frequency of Kawasaki disease by calculating cumulative relative risk. This study was approved by CHA University Institutional Review Board (GCI 2020-06-006). There was no active patient and public involvement in this study.

Between January 2016 to October 2019, the seasonality of HCoV peaked in December and January, with an average proportion of 2.9% (Figure 1). During the observed period, the annual incidence of Kawasaki disease ranged between 293 and 397 per 100 000 population and occurred least frequently in fall (September-November, regression coefficient = −0.23, $P = .005$). In DLNM, cumulative association of Kawasaki disease per 10% increase in the proportion of HCoV infection over 1 month lag with coronavirus was 0.50 (95% confidence interval: 0.16, 1.53), suggesting that seasonal variation in the frequencies of HCoV was not significantly associated with the change in the incidence of Kawasaki disease in South Korea.

Temporal association of various respiratory viruses and Kawasaki disease has been noted previously, however association remains unclear.[7] Our finding demonstrated no temporal association between HCoV and Kawasaki disease at the national level in South Korea. The concerns about the risk of inducing Kawasaki disease by HCoV do not, therefore, seem justified by our data. We found that the annual peak incidence of HCoV not coincided with the peak incidence of Kawasaki disease during distinct seasonal periods. There

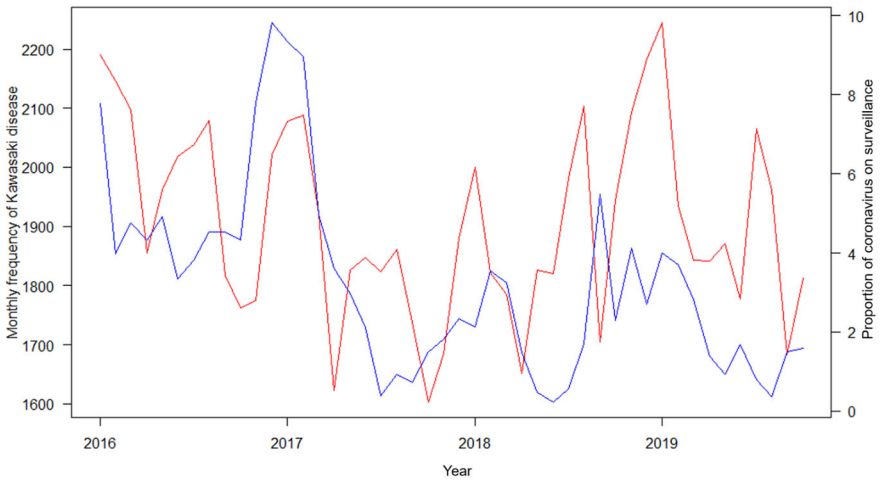

FIGURE 1 Monthly frequency of Kawasaki disease patients and the proportion of coronavirus detected in the national surveillance samples, South Korea, 2016 to 2019. Red lines are the monthly incidence of Kawasaki disease. Blue lines are the monthly proportion of coronavirus detected by the National Surveillance System

was no significant seasonal overlap in the peak incidence of HCoVs although this association was at the population level not at the individual patient level. This leads us to question whether the detection of an HCoV in a particular patient was associated with the occurrence of Kawasaki disease in the same patient. Clearly, more studies need to be done to elucidate their association at the individual level.

There are several limitations to this study. First, given the study is ecological in nature, aggregated de-identified laboratory data (individual HCoVs) and season from nationally notifiable disease surveillance system and insurance claim data that did not allow us to determine if one virus was detected in any particular person. Second, potential variation in frequency and quality of obtaining respiratory specimens may play a role in this finding causing a chance for misclassification bias. Third, other external factors such as environmental factors and temporal trends of different HCoVs were not accounted into the study design. However, our study method permitted us to study a relatively large number of cases at the national level to test our hypothesis. To our knowledge, this is the first study to summarize and appraise the association between HCoVs with Kawasaki disease at a national level while controlling the seasonality factor. We observed a no association between HCoVs and Kawasaki disease, which demonstrates no potential epidemiological linkage to explain the pathogenesis of Kawasaki disease.

Amid COVID-19 pandemic, the relation between the HCoV and Kawasaki disease is of special interest, owing to the clinical implication in children. To counteract these concerns, several places have started surveillance to detect cases of multisystem inflammatory disease in children (MIS-C). The results are awaited, but cases of MIS-C have been reported elsewhere. It is important to continue active and passive surveillance to monitor the adverse health outcomes in children with COVID-19 to assess the pathogenesis and clinical severity of severe acute respiratory syndrome coronavirus 2 in children exhibiting Kawasaki-like illness or multisystem inflammatory syndromes.

ACKNOWLEDGMENTS

The authors would like to thank the Ministry of Health and Welfare and the Health Insurance Review and Assessment Service of Korea for sharing national health insurance claims data. This study was supported by Hallym University Research Fund, 2019 (HRF-201912-009).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

YJC conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. S-AC designed the epidemiologic investigation protocols, collected data, carried out the initial analyses, and reviewed and revised the manuscript. HSA conceptualized and designed the study, coordinated, and critically reviewed the manuscript. YJC conceptualized and designed the study and oversaw the study process.

ORCID

Seung-Ah Choe http://orcid.org/0000-0001-6270-5020
Hyo Soon An http://orcid.org/0000-0001-6513-0592
Young June Choe http://orcid.org/0000-0003-2733-0715

REFERENCES

1. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis*. 2005;191(4):499-502.
2. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyama S, Taguchi F. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. *J Med Virol*. 2014;86(12):2146-2153.
3. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778.
4. Kim GB. Reality of Kawasaki disease epidemiology. *Korean J Pediatr*. 2019;62(8):292-296.

5. Kim JM, Jung HD, Cheong HM, et al. Nation-wide surveillance of human acute respiratory virus infections between 2013 and 2015 in Korea. *J Med Virol*. 2018;90(7):1177-1183.
6. Gasparrini A. Distributed lag linear and non-linear models in R: the package dlnm. *J Stat Softw*. 2011;43(8):1-20.
7. Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. *J Formos Med Assoc*. 2014;113(3):148-154.

How to cite this article: Choe S-A, An HS, Choe YJ. No temporal association between human coronavirus and Kawasaki disease: National data from South Korea. *J Med Virol*. 2021;93:585–587. https://doi.org/10.1002/jmv.26435