



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short communications

High population burden of Omicron variant (B.1.1.529) is associated with the emergence of severe hepatitis of unknown etiology in children

Hiroshi Nishiura*, Sung-mok Jung, Katsuma Hayashi

Graduate School of Medicine, Kyoto University, Kyoto, 6068503, Japan

ARTICLE INFO

Article history:

Received 4 May 2022

Revised 8 May 2022

Accepted 9 May 2022

Keywords:

Adenovirus

Causality

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Ecological study

Statistical association

Hepatitis

ABSTRACT

Objectives: To explore a potential country-based ecological link between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant (B.1.1.529) infection and an apparent current global outbreak of severe hepatitis of unknown etiology among children.

Methods: We examined country-level statistical associations between reported detection of one or more unexplained severe hepatitis cases in children and the cumulative number of Omicron (B.1.1.529) cases in 38 Organisation for Economic Co-operation and Development (OECD) member countries plus Romania.

Results: At least one focal hepatitis case was detected in 12 of the 39 countries included in our analysis. Numbers of confirmed Omicron cases reported in these 12 countries ranged from 4.4 to 11.9 million. Among the remaining 27 countries, this measure ranged from 0.5 to 5.5 million cases. Countries which reported focal hepatitis cases experienced higher precedent population burdens of Omicron cases relative to those which did not report any such hepatitis cases ($p=0.013$).

Conclusion: Prior exposure to Omicron variant (B.1.1.529) may be associated with an increased risk for severe hepatitis among children, indicating a critical need to conduct cofactor studies.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

The Omicron variant (B.1.1.529) emerged in late 2021, causing a widespread epidemic across the world, including in countries that had taken containment strategy with “zero-COVID” policy (Petersen et al., 2022). In industrialized countries that have experienced major extensive epidemics of Omicron, substantial fraction of the population was exposed, including children. For instance, a published seroepidemiological study in the United States indicated that approximately 75% of children have been infected by the end of February 2022 (Clarke et al., 2022).

Severe acute hepatitis of unknown etiology among children has been seen in various countries, including the United States and Europe (World Health Organization [WHO], 2022). Researchers have included adenovirus type F41 as a probable or possible cause or contributing causal factor based on microbiologic find-

ings (Marsh et al., 2022), and called for additional laboratory and epidemiological investigation (United Kingdom Health Security Agency [UKHSA], 2022a). An early Scottish review and analysis of available data deemed an infectious etiology as likely and included SARS-CoV-2 as well as adenovirus as potential co-factors to be further explored (Marsh et al., 2022).

Of note, SARS-CoV-2 was detected in 20 out of 169 hepatitis patients (WHO, 2022). Is this ratio too high to be easily dismissed or minimized? In reported hepatitis cases in children in England, the prevalence of COVID-19 among children with hepatitis was 11.8% (95% confidence interval [CI]: 7.1, 17.2), and the estimated prevalence of COVID-19 among the general child population in England was in a similar order during the peak Omicron wave there from March–April 2022. However, 11.8% is higher than 5–6% prevalence found by the Office of National Statistics Infection Survey result in late April (Office for National Statistics, 2022).

We aim here to investigate the potential link between infection with Omicron variant and severe hepatitis of unknown etiology among children. Using openly available statistical data, we seek to test for an ecological association between these variables.

* Correspondence to Hiroshi Nishiura at: Address: Yoshidakonoecho, Sakyo-ku, Kyoto city, Kyoto, 6068503, Japan, Tel: +81-75-753-4456; Fax: +81-75-753-4458.

E-mail address: nishiura.hiroshi.5r@kyoto-u.ac.jp (H. Nishiura).

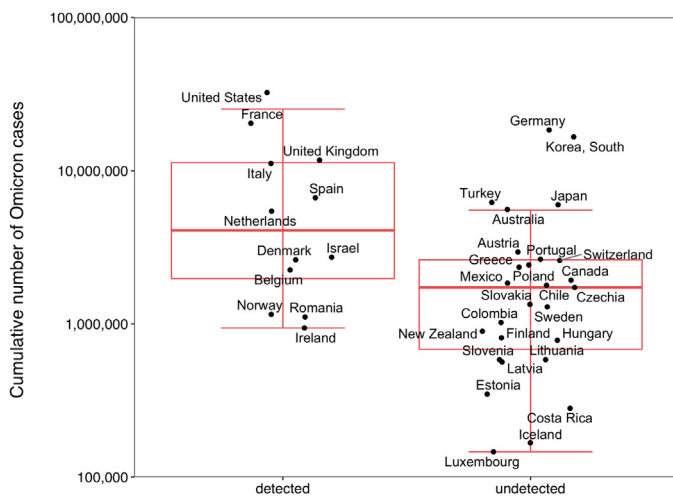


Figure 1. Cumulative number of Omicron cases in relation to the detection of severe acute hepatitis of unknown etiology among children.

A total of 38 countries that belong to the Organization for Economic Cooperation and Development plus Romania were included ($n=39$). Omicron (B.1.1.529) cases were calculated as the cumulative count from 1 December 2021 to 27 April 2022. Box plot measures the quartiles and median. Whiskers extend to 1st quartile - 1.5*(interquartile range) and 3rd quartile + 1.5*(interquartile range), respectively.

Materials and Methods

On April 27, 2022, we explored a statistical association between the detection of at least one hepatitis case and the cumulative number of Omicron cases (B.1.1.529), which was extracted from government reports among 38 countries that belong to the Organization for Economic Cooperation and Development (OECD). OECD countries were specifically investigated because of their capacity for virus sampling and laboratory testing, and other countries that do not OECD, only Romania was an exception, with a hepatitis case and was added to the analysis. We adhered to the WHO case definition, in which “probable case” is defined as a person aged 16 years and younger, presenting with an acute hepatitis (not caused by hepatitis A–E viruses) with serum transaminase >500 IU/l (aspartate aminotransferase or alanine transaminase) since October 1, 2021 (WHO, 2022).

Among these countries, we extracted government reports of confirmed cases as an indicator of the cumulative risk of Omicron infection. Considering the time at which Omicron variant started to be considered widespread, the cumulative number of COVID-19 cases from December 1, 2021–April 27, 2022 was used. The statistical association between the cumulative number of Omicron cases and countries with/without any reported hepatitis case was examined using Student’s t-test or Welch analysis of variance (ANOVA) after F-test.

Results

Of the 39 countries, 12 countries (30.8%) detected at least one hepatitis case, and their confirmatory diagnoses of Omicron cases ranged from 4.4–11.9 million. Among the remaining 27 countries, the cumulative number ranged from 0.5–5.5 million cases. Comparing these two groups with different variances ($P=0.026$ by F-test), Welch ANOVA indicated that countries with hepatitis cases were more likely to have experienced a greater number of Omicron cases ($P=0.013$, Fig. 1).

Comparing the cumulative incidence of Omicron cases per capita between two groups, the 12 countries with at least one hepatitis case again yielded greater mean incidence (21,868 per

100,000) than the 27 “no hepatitis” countries (18,532 per 100,000); however, the difference was not significant ($t=0.866$, $P=0.40$).

Discussion

Countries with greater SARS-CoV-2 Omicron variant infection frequencies according to the datasets we accessed, were more likely to have reported one or more cases of severe hepatitis of unknown etiology in children. We compared the presence of “reporting” of severe hepatitis, and thus found that our finding is consistent with marked difference in the absolute number of COVID-19 cases, not the incidence per capita.

Liver impairment has been documented to be induced by COVID-19 (Sivandzadeh et al., 2021), and scientific evidence of liver tropism with SARS-CoV-2 has been established, including molecular mechanisms (Wanner et al., 2022; Osborn et al., 2022). The high affinity of SARS-CoV-2 to the liver supports an existing working hypothesis (UK Health Security Agency, 2022a), suspecting an abnormal host response to adenovirus due to priming caused by a previous infection with SARS-CoV-2. Of course, our investigation has shown an ecological association at country levels; thus, the finding is prone to confounders. For instance, restriction of contact (i.e., maintaining social distance and wearing mask in indoor environment) can easily act as a confounder: when restrictions are eased, not only the risk of COVID-19 but also that of adenovirus would be elevated.

In the latest report from the United States, current co-morbid SARS-CoV-2 infection was ruled out in all of them, and none were found to have any documented previous infection with SARS-CoV-2 (Baker et al., 2022), whereas COVID-19 among children aged 3 years and younger tend to be asymptomatic or clinically very mild. Examining coinfection dynamics among diagnosed hepatitis cases in England over time, coinfections during peak period of hepatitis cases were found and a small number of adenovirus negative cases with COVID-19 were identified (UK Health Security Agency, 2022b).

An important limitation is that Omicron infections among children only have not been monitored consistently across countries; instead, we examined the cumulative number of Omicron cases for the entire population. Despite this limitation, the present ecological study has shown that a previous exposure to the Omicron variant may be associated with an increased risk of severe hepatitis among children, indicating a critical need to conduct cofactor studies (Marsh et al., 2022; UK Health Security Agency, 2022b). Such studies should explore, without limitation, the possible involvement of extrapulmonary manifestations of COVID-19 as an important factor in inducing severe acute hepatitis among children.

Acknowledgments

HN received funding from Health and Labour Sciences Research Grants (20CA2024, 20HA2007, 21HB1002 and 21HA2016), the Japan Agency for Medical Research and Development (JP20fk0108140, JP20fk0108535, and JP21fk0108612), the JSPS KAKENHI (21H03198), and the Japan Science and Technology Agency SICORP program (JP-MJSC20U3 and JPMJSC2105). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Mr Jim Reynolds for closely editing the revised manuscript.

Conflict of interest

We declare that we have no conflict of interest.

Ethical approval statement

The present study used publicly available data from the Johns Hopkins University (<https://github.com/CSSEGISandData/COVID-19>), and all data were de-identified prior to analysis. Analyzing anonymous data did not require ethical approval.

References

- Baker JM, Buchfellner M, Britt Wet al. Acute hepatitis and adenovirus infection among children – Alabama, October 2021–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:638–40.
- Clarke KEN, Jones JM, Deng Yet al. Seroprevalence of infection-induced SARS-CoV-2 antibodies – United States, September 2021–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:606–8.
- Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, Henderson D, Divala T, Currie S, Yirrell D, Lockhart M, Rossi MK, Phin N. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. *Euro Surveill* 2022;27.
- Office for National Statistics, Coronavirus (COVID-19) infection survey, UK. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurvey/pilot/22april2022>, 2022 (accessed 28 April 2022).
- Osborn Julie, Szabo Sara, Peters Anna. Pediatric Acute Liver Failure Due to Type 2 Autoimmune Hepatitis Associated With SARS-CoV-2 Infection: A Case Report. *JPGN Reports* 2022;3(2):e204–e204. doi:10.1097/PG9.0000000000000204.
- Petersen E, Ntoumi F, Hui DS, Abubakar A, Kramer LD, Obiero C, Tambyah PA, Blumberg L, Yapi R, Al-Abri S, Pinto TCA, Yeboah-Manu D, Haider N, Asogun D, Velavan TP, Kapata N, Bates M, Ansumana R, Montaldo C, Mucheleng'anga L, Tembo J, Mwaba P, Himwaze CM, Hamid MMA, Mfinanga S, Mboera L, Raj T, Akiillu E, Veas F, Edwards S, Kaleebu P, McHugh TD, Chakaya J, Nyirenda T, Bockarie M, Nyasulu PS, Wejse C, Muyembe-Tamfum JJ, Azhar EI, Maeurer M, Nachega JB, Kock R, Ippolito G, Zumla A. Emergence of new SARS-CoV-2 Variant of Concern Omicron (B.1.1.529) - highlights Africa's research capabilities, but exposes major knowledge gaps, inequities of vaccine distribution, inadequacies in global COVID-19 response and control efforts. *Int J Infect Dis* 2022;114:268–72.
- Sivandzadeh GR, Askari H, Safarpour AR, Ejtehadi F, Raeis-Abdollahi E, Vaez Lari A, Abazari MF, Tarkesh F, Bagheri Lankarani K. COVID-19 infection and liver injury: clinical features, biomarkers, potential mechanisms, treatment, and management challenges. *World J Clin Cases* 2021;9:6178–200.
- UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England; 2022a https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1071198/acute-hepatitis-technical-briefing-1_4_.pdf accessed 28 April 2022.
- UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England; 2022b https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1073704/acute-hepatitis-technical-briefing-2.pdf accessed 7 May 2022.
- Wanner N, Andrieux G, Badia-i-Mompel Pet al. Molecular consequences of SARS-CoV-2 liver tropism. *Nat Metab* 2022;4:310–19.
- World Health Organization, Multi-Country – acute, severe hepatitis of unknown origin in children. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376>; 2022 (accessed 28 April 2022).