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Regional assessment is useful for identifying populations at high-risk of hepatitis B virus transmission: A nationwide analysis of population-based surveillance including the COVID-19 pandemic era

Kazuya Okushin[1,2,§], Hideki Aizaki[3,§], Kazuhiko Ikeuchi[4], Toshiyuki Kishida[4], Akira Kado[2], Mitsuhiro Fujishiro[2], Takeya Tsutsumi[1,4], Tomoyuki Takura[5,6], Hiroshi Yotsuyanagi[7,*]

[1] Department of Infection Control and Prevention, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;
[2] Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;
[3] National Institute of Infectious Diseases, Japan Institute for Health Security, Tokyo, Japan;
[4] Department of Infectious Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;
[5] Department of Healthcare Economics and Health Policy, The University of Tokyo, Tokyo, Japan;
[6] Department of Health Care Services Management, Nihon University School of Medicine, Tokyo, Japan;
[7] Division of Infectious Diseases, Advanced Clinical Research Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan.

Abstract: Prevention of new infections is important for the elimination of viral hepatitis B. Assessing the impact of the Coronavirus disease 2019 (COVID-19) pandemic on hepatitis B incidence is important for future infection control measures. A recent hospital-based questionnaire survey implied that a regional assessment in each country would be useful for establishing new preventive measures. This retrospective study examined publicly reported national data of patients diagnosed with acute hepatitis B in Japan between 2015 and 2022. The transition of total numbers, incidence, sex, and age distribution in each year were analyzed. Comparisons were made between populous and non-populous prefectures before and during the COVID-19 pandemic (2015–2019 *vs.* 2020–2022). A median of 210.0 patients with acute hepatitis B (interquartile range [IQR], 176.5–231.2 patients) were reported in each year. The number and incidence of acute hepatitis B cases significantly decreased during the pandemic, and the impact of COVID-19 was pronounced in males, especially in non-populous prefectures. Populous prefectures had significantly higher incidence in males compared with non-populous prefectures (3.55 [3.26–4.07] *vs*. 2.30 [1.78–2.64] cases per 1,000,000 people per year; $p = 0.004$), whereas those of females did not. Regarding patient age, the proportions of patients aged in their 20s, especially females, were higher in populous prefectures. These results may reflect differences in lifestyle, including sexual behaviors, in each population with the interaction of the COVID-19 pandemic. Identifying high-risk populations in each area and establishing a tailored strategy to eliminate viral hepatitis would be useful for countries worldwide.

***Keywords*:** acute hepatitis B, national data, regional assessment, COVID-19, sexually transmitted disease

Introduction

The elimination of viral hepatitis, including hepatitis B, is a major global health goal. In 2016, the World Health Organization (WHO) published a global sector strategy for viral hepatitis elimination, which aimed to reduce new hepatitis infections by 90% and deaths by 65% by 2030 worldwide, including in developing countries (*1*). Vaccination successfully prevents the vertical and horizontal transmission of hepatitis B virus (HBV) (*2*), and nucleoside/nucleotide analogs efficiently suppress HBV replication (*3,4*). Consequently, the number of active viral carriers has decreased in Japan (*5*). To achieve the remaining major focus in eliminating viral hepatitis, namely the prevention of new infections, means of identifying high-risk populations are urgently needed.

The Coronavirus disease 2019 (COVID-19) pandemic has had profound effects on global healthcare systems (*6*). Regarding infectious diseases, the number of reported cases of most infections decreased during the COVID-19 pandemic (*7*). We recently reported a questionnaire-based survey at nationwide tertiary care centers to reveal a real-world trend in the incidence of acute hepatitis B in Japan, presenting a significant decrease in the number of such cases in Japan (*8*); these results were consistent with those reported in foreign countries (*9-11*). However, the number of reported cases of sexually transmitted diseases (STDs) in Japan was relatively stable during

the COVID-19 pandemic and increased only in the later phase (*12-14*). Acute viral hepatitis has an aspect of a STD, and new measures are urgently needed to control this rebound.

The proceeding questionnaire-based survey also revealed that the sex ratio of acute viral hepatitis cases differed regionally; namely, populous prefectures, including Tokyo, the most populous capital city in Japan, had a higher proportion of male patients than non-populous prefectures (*8*). We assumed that detailed data, namely, age and incidence in each area, could provide further insights into the development of tailored strategies for the prevention of rebounding acute viral hepatitis.

In this study, we analyzed publicly reported national data concerning acute viral hepatitis B in the Infectious Diseases Weekly Report (IDWR) published by the National Institute of Infectious Diseases (NIID) in Japan (*15,16*).

Patients and Methods

Study design and data sources

This retrospective study examined publicly reported national data concerning acute hepatitis B infections in Japan between 2015 and 2022. In Japan, a doctor who diagnoses a patient with newly diagnosed acute viral hepatitis B is legally required to report and register details of the patient with the National Epidemiological Surveillance of Infectious Diseases (NESID) system, which is run jointly by the NIID, prefectural and municipal public health institutes and public health centers, and the Ministry of Health, Labour and Welfare. In the NESID system, acute hepatitis B is defined as the detection of IgM anti-HBc antibodies (excluding cases of acute exacerbation in obvious carriers). The number of cases classified according to sex or reported prefecture was obtained from the NIID website as IDWR (*15,16*). Population data were obtained from the Ministry of Health, Labour and Welfare website (*17*).

This study was conducted in accordance with the principles of the Declaration of Helsinki and complied with the ethical guidelines for medical and health research involving human subjects established by the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor, and Welfare. This study was approved by the Research Ethics Committee of the Faculty of Medicine, the University of Tokyo (approval number: 2024504NIe).

Regional assessments

Japan is divided into 47 prefectures that are grouped into eight regions based on geographical and historical factors. These regions are: Hokkaido, Tohoku (including Aomori, Iwate, Miyagi, Akita, Yamagata, and Fukushima); Kanto-Shinetsu (including Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Yamanashi, and Nagano); Tokai-Hokuriku (including Toyama, Ishikawa, Gifu, Shizuoka, Aichi, and Mie); Kinki (including Fukui, Shiga, Kyoto, Osaka, Hyogo, Nara, and Wakayama); Chugoku (Tottori, Shimane, Okayama, Hiroshima, and Yamaguchi); Shikoku (including Tokushima, Kagawa, Ehime, and Kochi); and Kyushu (including Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, and Okinawa).

We selected Tokyo (the most populous city and one of the centers of Kanto-Shinetsu region: 13,443,000 persons in 2022), Kanagawa (the second-most populous city and one of the centers of Kanto-Shinetsu region: 8,991,000 persons), Osaka (the third-most populous city and the center of the Kinki region: 8,524,000 persons), Aichi (the fourth populous city and the center of the Tokai region: 7,228,000 persons), and Fukuoka (the nineth-most populous city and the center of Kyushu region: 5,030,000 persons), as populous prefectures based on their population density and regional characteristics.

Statistical analysis

Data are presented as medians and interquartile ranges (IQRs) for quantitative variables, and numbers and percentages for qualitative variables. For comparisons between two categories, namely before and during the COVID-19 pandemic (2015–2019 *vs.* 2020–2022), and populous prefectures and non-populous prefectures, Welch's *t*-test was used to assess statistical significance. The proportion of 20s in each group is presented with 95% confidential intervals (CIs) calculated using the Wilson method, and the Chi-squared test was used to assess statistical significance. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software v.4.3 and later (R Foundation, Vienna, Austria, *http://www.r-project.org*).

Results

Trends in national incidence of acute hepatitis B infection

In total, a median of 210.0 patients with acute hepatitis B (interquartile range [IQR], 176.5–231.2 patients) were reported in each year, with the proportion of males remaining relatively constant throughout the period at a median of 81.7% (IQR, 78.5%–84.4%) (Figure 1A). During the COVID-19 pandemic, the number of patients significantly decreased during 2020–2022 compared to that during 2015–2019 (median [IQR] = 148.0 [142.0–167.0] patients *vs.* 228.0 [214.0–241.0] patients; $p = 0.02$).

The median incidences were 1.68 (IQR, 1.43–1.85), 2.79 (IQR, 2.29–3.08), and 0.62 (IQR, 0.50–0.73) cases per 1,000,000 people per year for total, males, and females, respectively (Figure 1B). During the COVID-19

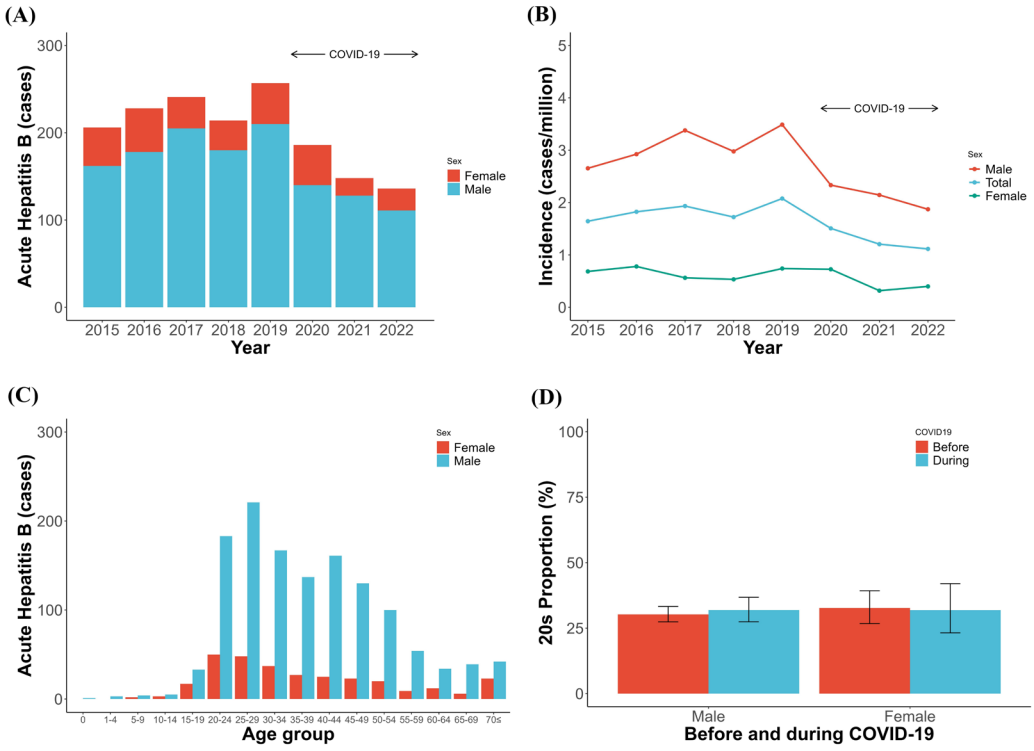

Figure 1. Impact of the COVID-19 pandemic on the transition of total number, incidence, and age range of acute hepatitis B in Japan. (A) Number of acute hepatitis B cases in each year; **(B)** Incidence of acute hepatitis B in each year; **(C)** Age range of acute hepatitis B cases in an entire period; **(D)** Proportion of 20s in the eras before and during the COVID pandemic. The proportion of 20s and 95% confidence intervals (Wilson method) in each group are shown.

pandemic, the incidences of total and male patients significantly decreased during 2020–2022 compared with that of 2015–2019 (median [IQR] = 1.21 [1.16–1.36] *vs.* 1.82 [1.72–1.93] cases per 1,000,000 people per year; $p = 0.02$, and 2.15 [2.01–2.24 *vs.* 2.98 [2.92–3.38] cases per 1,000,000 people per year; $p = 0.004$), whereas those of females did not (median [IQR] = 0.40 [0.36–0.56] *vs.* 0.68 [0.56–0.74] cases per 1,000,000 people per year; $p = 0.28$).

In terms of age at diagnosis, there was a peak in the number of patients in their 20s for both sexes (Figure 1C). The proportion of patients in their 20s was consistent before and during the COVID-19 pandemic (30.3% [95% CI 27.4–33.3] *vs.* 31.9% [27.4–36.8]; $p = 0.60$ in males and 32.7% [26.7–39.3] *vs.* 31.9% [23.2–42.0]; $p = 0.99$ in females, respectively, Figures 1D).

Regional assessment of incidence of acute hepatitis B

We evaluated the total number and incidence of acute hepatitis B infections in each prefecture (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=101*). Tokyo, the capital and the most populous city, had both the highest number of patients (in total 394 patients per eight years) and the highest annual incidence (median [IQR] = 3.79 [3.09–4.37] cases per 1,000,000 people per year). Choropleth maps of the population in 2022 and the total number of acute hepatitis B cases per eight years in each prefecture were described in Figure 2A and 2B, respectively.

To highlight the impact of population, we selected populous prefectures (Tokyo, Kanagawa, Osaka, Aichi, and Fukuoka) and compared them with other prefectures. The number of patients with acute hepatitis B were decreased both in the populous and non-populous prefectures during 2020–2022 compared with that of 2015–2019 (median [IQR] = 70.0 [61.0–81.0] patients *vs.* 100.0 [94.0–109.0] patients; $p = 0.09$ in the populous prefectures, and 84.0 [81.0–89.0] patients *vs.* 120.0 [119.0–131.0] patients; $p = 0.001$ in the non-populous prefectures, respectively, Figure 3A and 3B). Similar to our previous report, the proportion of males was relatively higher in populous prefectures than in non-populous prefectures (median [IQR] = 81.3% [80.6%–85.1%] *vs.* 80.8% [77.3%–83.1%], respectively; $p = 0.16$).

The populous prefectures had significantly higher infection incidence in the total and male populations compared with non-populous prefectures (median [IQR] = 2.14 [1.93–2.36] *vs.* 1.45 [1.15–1.52] cases per 1,000,000 people per year in total population; $p = 0.005$, and 3.55 [3.26–4.07] *vs.* 2.30 [1.78–2.64] cases per 1,000,000 people per year in male population; $p = 0.004$), whereas those of females did not (median [IQR] = 0.77

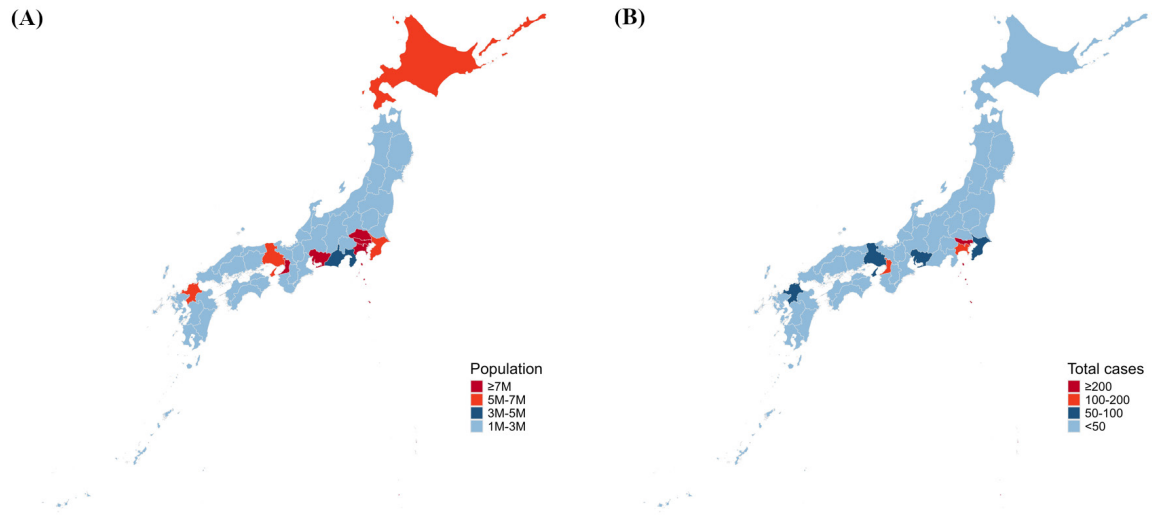

Figure 2. Choropleth maps of population and total number of acute hepatitis B cases in each prefecture in Japan. (A) Choropleth map of population in 2022 in each prefecture; **(B)** Choropleth map of total number of acute hepatitis B per eight years in each prefecture.

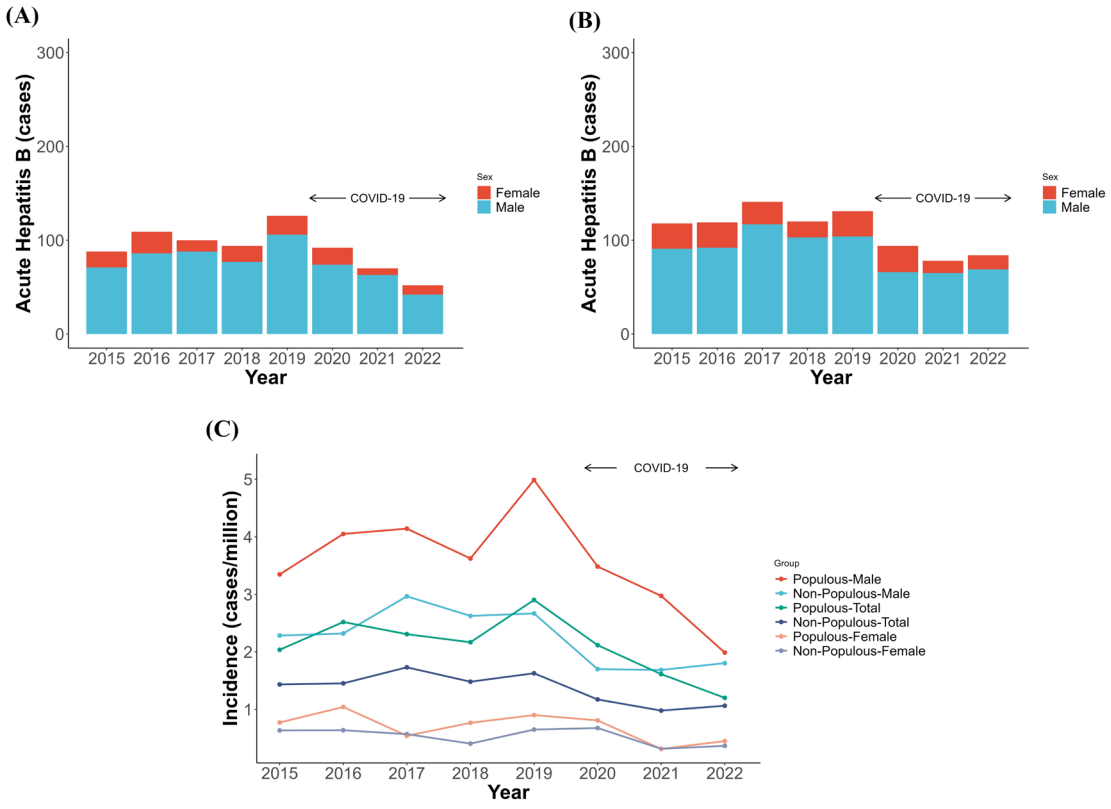

Figure 3. Transition of total number and incidence of acute hepatitis B in populous and non-populous prefectures in Japan. (A) Number of acute hepatitis B cases in populous prefectures; **(B)** Number of acute hepatitis B cases in non-populous prefectures; **(C)** Incidence of acute hepatitis B in populous and non-populous prefectures.

[0.52–0.83] *vs.* 0.61 [0.40–0.64] cases per 1,000,000 people per year; $p = 0.12$, Figure 3C). Interestingly, regarding the impact of the COVID-19 pandemic on changes in incidence, the incidence of males in the non-populous prefectures was significantly decreased (median [IQR] = 2.63 [2.32–2.67] and 1.70 [1.70–1.75] cases per 1,000,000 people per year in 2015-2019 and 2020–2022, respectively; $p = 0.002$), and that in the populous prefectures was relatively decreased (median [IQR] = 4.05 [3.62–4.14] and 2.98 [2.48–3.23] cases per 1,000,000 people per year in 2015–2019 and 2020–2022, respectively; $p = 0.09$), whereas those of females did not.

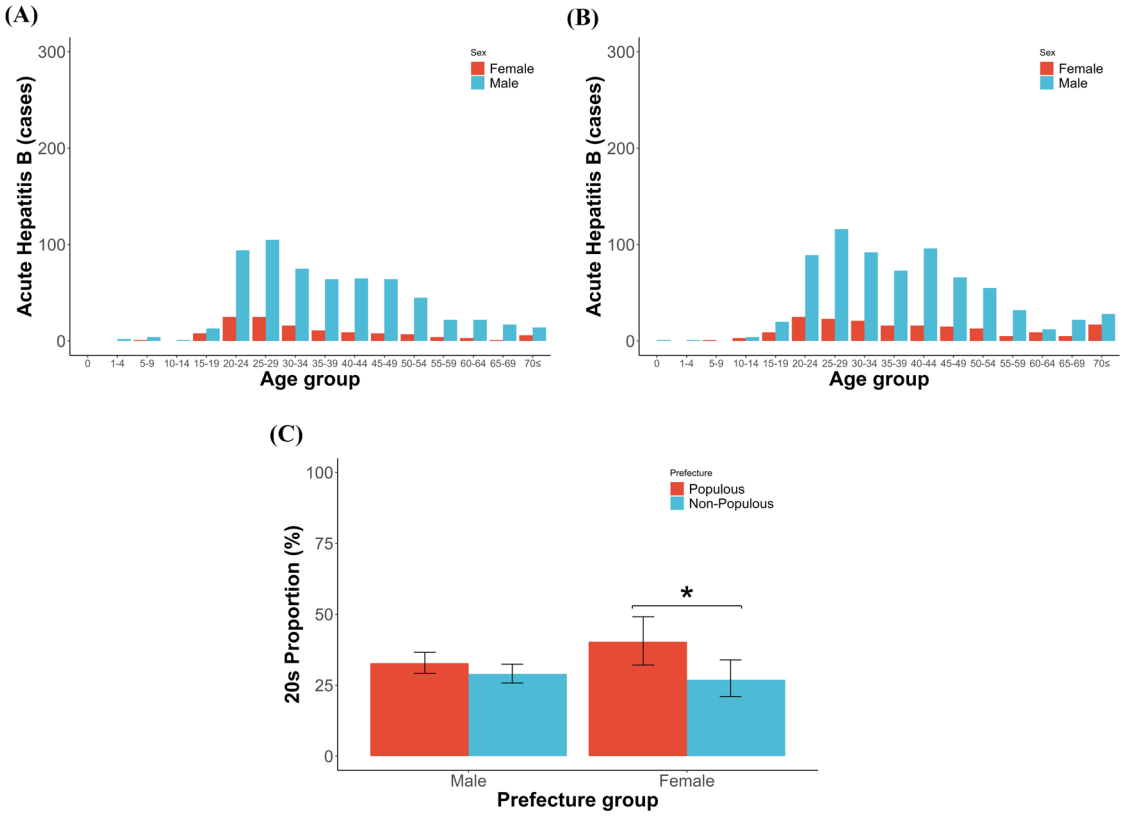

Figure 4. Age range of acute hepatitis B cases in populous and non-populous prefectures in Japan. (A) Age range of the acute hepatitis B cases in populous prefectures; **(B)** Age range of the acute hepatitis B cases in non-populous prefectures; **(C)** Proportion of 20s in populous and non-populous prefectures. The proportion of 20s and 95% confidence intervals (Wilson method) in each group are shown. *$p < 0.05$.

The distributions of patients' ages were described in Figure 4A for populous prefectures and Figure 4B for the non-populous prefectures. Interestingly, the proportions of 20s patients were higher in the populous prefectures than those in the non-populous prefectures, especially in females (32.8% [95% CI: 29.2–36.6] *vs.* 29.0 [25.8–32.4]; $p = 0.15$ in males and 40.3% [32.1–49.1] *vs.* 27.0% [21.0–33.9]; $p = 0.02$ for females, Figures 4C).

Discussion

We analyzed national data surrounding the characteristics of patients with acute hepatitis B in Japan, focusing on the impact of the COVID-19 pandemic and regional differences. The number and incidence of acute hepatitis B cases significantly decreased during the COVID-19 pandemic, and the impact of COVID-19 was pronounced in males, especially in non-populous prefectures. The incidence of males in populous prefectures was significantly higher than that in non-populous prefectures, whereas that of females was similar between the groups. In populous prefectures, the proportion of younger patients, especially females, was higher than that in non-populous prefectures.

Employing the number of patients reported from each prefecture and the population each year, we calculated the annual incidence in addition to the numbers of patients in each prefecture. The incidence of acute hepatitis B cases significantly decreased during the COVID-19 pandemic, similar to previous reports from other countries (*9,10*). Interestingly, although the incidence in males was significantly decreased during the COVID-19 pandemic, that in females did not. In general, COVID-19 restrictions were associated with a reduction in sexual activity including in Japan (*18-20*). Focusing on the practice of sexual behaviors, Li *et al.* reported that the number of sexual partners and risky sexual behaviors – defined as inconsistent condom use, casual sexual partnerships, or multiple sexual partnerships – decreased more in men than in women (*21*). In this context, a higher incidence of acute hepatitis B infections is noted among men who have sex with men (MSM) (*22*). It has also been reported that MSM reduced their risky sexual behavior during the COVID-19 pandemic (*23*). Although we had no data regarding sexuality in this study, it is suspected that the decreased incidence in males might be partly caused by MSM. Overall, the sex differences in incidence transition in our study might be due to differences in sexual behavior between males and females.

We also focused on regional differences between populous and non-populous prefectures in terms of incidence, sex ratio, and age distribution of patients with acute hepatitis B. In populous prefectures, a significantly higher incidence of males, a relatively higher male ratio, and a significantly higher proportion of people in their 20s, especially females, was observed compared with non-populous prefectures. Regarding the male population, we previously reported that hepatitis C virus/human immunodeficiency virus-coinfected patients are more likely to be male, have other STDs, and live in Tokyo, the most populous city in Japan (*24*). The higher incidence of male in populous prefectures might reflect a population of sexually active patients, including MSM. Interestingly, the decline in male incidence was more pronounced in non-populous than in populous prefectures when the effects of the COVID-19 pandemic and regional differences were considered together. These time series and regional differences could be caused not only by differences in the population at risk, but also by changes in lifestyle, including inter-prefectural travel, in each area during the COVID-19 pandemic period, especially when behavioral restrictions were prominent (*25-28*), although the changes in sexual behavior have not been sufficiently assessed. Regarding females, the difference in the proportion of ages between populous and non-populous prefectures represents a novel finding. In populous prefectures, females in their 20s should be considered as a high-risk population. In contrast, in non-populous prefectures, HBV infections occurred evenly across a wide range of age groups, including those aged > 70 years. These results indicate the potential of targeted and specific population-based approaches for the prevention and screening of infected persons depending on the characteristics of a given region. These results may have implications for the establishment of individual measures, including vaccinations in populous and non-populous areas, not only in Japan, but also in many other countries.

Our study had certain limitations. First, although information concerning transmission routes is registered in the NESID system, the raw data are not publicly available owing to regulations in Japan. However, a recent public summary reported that sexual contact is an abundant transmission route (*16*). Second, although case reporting is legally required, some cases may be missing because surveillance data are on a reported basis.

In conclusion, national data regarding acute hepatitis B infection in Japan clearly revealed the impact of the COVID-19 pandemic and of epidemiological differences, such as a higher incidence of males and a higher proportion of people in their 20s, especially females, in populous prefectures. Identifying high-risk populations is necessary to establish tailored strategies for eliminating viral hepatitis in each area. This research suggests that to develop rapid and effective measures for hepatitis prevention, it would be useful to translate global and national goals into targets for specific populations, including regions and age groups.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Hiroshi Yotsuyanagi, Division of Infectious Diseases, Advanced Clinical Research Center, Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.
E-mail: yotsudid@ims.u-tokyo.ac.jp