

Title:

Effect of COVID-19 on hepatitis B and C virus countermeasures: hepatologist responses from nationwide survey in Japan

Authors:

Md Razeen Ashraf HUSSAIN^{a*}, Lindsey HIEBERT^{a,b*}, Aya SUGIYAMA^a, Serge OUOBA^{a,c}, Bunthen E^{a,d}, Ko KO^a Tomoyuki AKITA^a, Shuichi KANEKO^e, Tatsuya KANTO^f, John W. WARD^b, Junko TANAKA^{a†}

Affiliation:

^a Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan

^b Coalition for Global Hepatitis Elimination, The Task Force for Global Health, United States of America

^c Unité de Recherche Clinique de Nanoro (URCN), Institut de Recherche en Science de la Santé (IRSS), Nanoro, Burkina Faso

^d Payment Certification Agency, Ministry of Health, Cambodia

^e Department of Gastroenterology, Kanazawa University Graduate School of Medical Science, Japan

^f The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Japan

* Co-first authors. MR and LH contributed equally to this work.

†Corresponding author:

Junko Tanaka, PhD

Professor, Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/hepr.13819](#).

This article is protected by copyright. All rights reserved.

1-2-3, Kasumi, Minami-ku, Hiroshima-shi, 734-8551, Japan

Tel: 082-257-5161 / Fax: 082-257-5164

E-mail: jun-tanaka@hiroshima-u.ac.jp

Word count of manuscript: 3005 words

Running Title:

COVID-19 effect on HBV and HCV in Japan

Abstract

Aim:

Achieving hepatitis B virus (HBV) and hepatitis C virus (HCV) elimination requires continuous and sustained high volumes of diagnosis and treatment which have been affected by the ongoing COVID-19 pandemic. This study assessed COVID-19 effect on hepatitis-related services in Japan and compare Japan's situation with global survey.

Methods:

We conducted an online cross-sectional questionnaire survey of hepatologist of the Japan Society of Hepatology from August to October 2021 by using the same questionnaire from which a survey was conducted globally to address the COVID-19 effect on hepatitis-related services. Hepatologists responded based on own impression of their affiliated institutions.

Results:

A total of 196 hepatologists participated from 35 prefectures including 49.5% were in managerial positions. Around 40% survey participants reported a 1-25% decline in HBV and HCV screening and confirmatory testing. In addition, 53.6% and 45.4% reported no decline in HBV and HCV treatment initiation, respectively. Comparing any level of decrease, less decline was observed in Japan for screening (HBV: 51% vs 56.3%, HCV: 51% vs 70.9%) and treatment initiation (HBV: 32.7% vs 52.4%, HCV: 41.8% vs 66%) from global survey. However, Patient anxiety/fear (67.4%), and loss of staff due to COVID-19 response (49.0%) were reported as challenges to resume services to pre-COVID-19 levels.

Conclusion:

Although in Japan all-inclusive decline in HBV and HCV related services were lower

than in other countries, a greater decline was observed in HBV and HCV screening and diagnosis than in treatment initiation. Prolonged anxiety/fear among patients, loss of staffs and facilities on COVID-19 responses must be addressed to achieve the hepatitis elimination by 2030.

Keywords: HBV, HCV, COVID-19, Effect, Response, Japan

Introduction

In 2016, the World Health Organization (WHO) set goals to eliminate hepatitis B virus (HBV) and hepatitis C virus (HCV) by 2030. Achievement of these goals require substantial scale-up of HBV and HCV screening and treatment that is sustained over time.(1, 2) In Japan, since 1995-2000 hepatitis B and hepatitis C have been recognized as major health problems particularly among those persons born before the adoption of routine hepatitis B vaccination of infants and recipients of blood and blood products before routine screening of the blood supply.(3) As for viral hepatitis countermeasure, several initiatives have been adopted by government such as free HBV and HCV testing and screening among ≥ 40 years old people and medical expense subsidy system for antiviral treatment of HBV and HCV under the Basic Act on Hepatitis Measures (2010).(3-6) In addition, the National Campaign Project for Hepatitis Measures (2013) for awareness and routine three doses hepatitis vaccine to all infant (2017) contributed to gradual decreases in the incidence and prevalence of HBV and HCV infections.(7, 8) Indeed, until 2020, Japan was moving in the right direction to achieve HBV and HCV elimination by 2030.(9-11)

Unfortunately, on 31 December 2019, China reported 27 cases of a new viral infection with unknown etiology in Wuhan City of Hubei Province.(12) On 11 February 2020, this disease was officially named Coronavirus disease- 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).(13) The virus quickly spread within China and to 24 additional countries where in Japan the first case was detected on 15th of January 2020.(14) On 11th of March 2020, the World Health Organization (WHO) Director-General officially declared COVID-19 as a pandemic. The COVID-19 pandemic

Accepted Article

hampered routine functions of the health care system, including access to HBV and HCV treatment, care and prevention.(15-21) In 2020 (August-December), the Coalition for Global Hepatitis Elimination, a program of The Task Force for Global Health, conducted a global survey on the impact of COVID-19 on the interruption of HBV and HCV prevention, testing, treatment and care.(22) The survey results highlighted a decline in HBV and HCV screening, confirmatory and baseline evaluation testing, and treatment across countries. Survey respondents were from 44 countries. However, Japan was not represented. Besides, several studies have done related to COVID-19 and liver disease(23-26), but there is no study on the COVID-19 impact on HBV and HCV related services in Japan.

This study assesses the impact of COVID-19 on hepatitis prevention, testing, and treatment in Japan and to understand the situation of Japan compared to other countries in global survey. This survey conducted by the Ministry of Health, Labour and Welfare (MHLW) Hepatitis Policy Research Project (Epidemiology Group, Expansion Group, Hepatitis ICT Group) and the Task Force for Global Health, in cooperation with the Japan Society of Hepatology (JSH).

Methods

Survey design

This study was an analytic cross-sectional questionnaire developed in Microsoft Forms. The questionnaire was adapted from the Task Force for Global Health survey.(22) A total of 46 questions aimed to assess the COVID-19 pandemic's impact on access to HBV and HCV services and the response of programs in service delivery (Supplementary Table 1). The survey areas included i) delivery of HBV and HCV related services during COVID-

19, ii) challenges to resuming services to pre-COVID-19 levels and COVID-19 mitigation strategies, iii) clinical involvement in the response to COVID-19 and iv) the potential benefits of the COVID-19 response on the hepatitis system (Figure 1).(22) Several questions were added, modified, and rearranged based on the Japanese context for each survey area. Electronic versions of the questionnaire were developed in both English and Japanese.

Targeted participants of the survey were medical doctors (hepatologist) affiliated with the Japan Society of Hepatology (JSH) which was established in 1959. The questionnaire web link was disseminated by JSH to members via e-mail as well as advertised on the official JSH website. Besides JSH dissemination, authors additionally sent 30 invitations about the survey to the head of regional core centers for treatment of hepatitis in all prefectures and the members of MHLW Hepatitis Policy Research Project (Epidemiology Group, Expansion Group, Hepatitis ICT Group) by e-mail. The survey was open from 24 August 2021 to 03 October 2021 (40 days). During our survey period fifth wave was ongoing in Japan.

Survey analysis

Microsoft Excel for Microsoft 365 MSO (Version 2112 Build 16.0.14729.20254) was used to store survey responses. Statistical analyses were conducted using JMP15.0.0 software (SAS Institute Inc., Cary, NC, USA). Descriptive analyses of background characteristics of participants and responses were conducted; frequencies and percentages were calculated and reported. Chi square-tests were performed to compare data between the Japan survey and global survey(22), and *p* values less than 0.05 were regarded as statistically significant.

Ethical consideration

This was a cross-sectional survey which received ethics approval for data collection and analysis. The ethics committees for epidemiological research at Hiroshima University waived the need for further informed consent, as no patient or patient health information was collected, and approved the study (approval number, E-2530). All study activities were performed in accordance with relevant guidelines and regulations.

Results

Survey respondents

A total of 196 medical doctors (hepatologists) were responded affiliated with JSH. Participants were from 35 of the 47 prefectures of Japan. (Figure 2) Among participants, 52.6% was affiliated with university hospitals, 27.6% with public hospitals, 14.3% with private hospitals, 3.6% with clinics, and 1.0% from government agencies and other institutions. (Table 1) About half of respondents (49.5%) held managerial positions related to liver disease or hepatitis control at their institution. Hepatologists responded based on impression of their own institutions.

HBV and HCV related screening, confirmatory testing and treatment

Declines were noted at nearly every stage of HBV and HCV screening, diagnosis, and treatment during the month of highest COVID-19 impact, compared to pre-COVID-19 levels. Declines in HBV and HCV screening and confirmatory testing were greater than declines in than treatment. A 1-25% decline in screening rates was reported by 38.8% for HBV and 39.8% for HCV while 8.7% and 7.7% reported decrease of 26-50%, respectively. For HBV and HCV confirmatory testing, 43.9% and 43.4% reported between a 1-25% level of patient volume decline, respectively. In comparison, 28.1% and 32.1% participants reported a 1-25% decrease in HBV and HCV treatment. About 40%

of participants reported a 1-25% decrease in patient volume for monitoring in HBV and HCV treatment. However, 60.7% of medical doctors reported no decline in SVR 12 for HCV treatment. (Figure 3)

No major supply chain disruption related to HBV and HCV was noticed. Syringe-injection equipment (7.1%) was reported as supply chain disruption during COVID-19 period. On others (free description), mask, disinfection equipment and PPE (18.9%), sedative and drugs (4.6%) were reported as disruption of supply chain during COVID-19. Unfortunately, 11.7% of respondents indicated that during the survey period supply chain disruptions remained on-going. 73.5% participants responded that program management meetings related to hepatitis were cancelled during the COVID-19 pandemic in Japan.

Other services deferred during COVID-19

The majority of respondents reported delaying imaging includes all kind of diagnosis of liver disease including HCC (65.8%), lab testing (68.4%), HCC screening (55.1%) and gastrointestinal endoscopy (87.2%) during the COVID-19 pandemic. As part of public awareness and lectures, 38.8% of clinicians reported on deferring nutritional guidance on diet for patients at hospital and 55.6% deferred liver-disease related lectures for patients and the public in the greatest impact month of COVID-19. (Table 2)

For HCC-related services, 26.0% and 25.5% of clinicians reported a decline between 1-25% in patient volumes receiving HCC treatment and monitoring of HCC patients, respectively. Only 2.0% reported a decline of 26-50% in patients receiving and monitoring HCC patients. (Figure 3) For drug addiction treatment, 30.1% of respondents reported no decline in patient volumes during the highest impact COVID-19 month compared to a typical month pre-COVID. Only 10.2% of participants reported a decline of 1-25% in patient volumes receiving drug addiction treatment.

Challenges to resume services and mitigation strategies

Patient anxiety and fear (67.4%), limited availability of staff (46.4%), loss of staff to COVID-19 response activities (49.0%), loss of clinic space to COVID-19 response activities (34.7%) and loss of funding (16.3%) were reported as key challenges to resuming services to pre-COVID-19 levels. Of note, 11.7% of clinicians described no challenges to resuming hepatitis services. (Table 3)

Respondents reported adopting strategies to mitigate the COVID-19 situation, including telemedicine. More than 55% of clinicians responded that they relied on audio-only telemedicine appointment, while 9.7% conducted telemedicine appointments with video via phone. However, 28.6% reported no use of telemedicine. Beyond telemedicine, 59.2% extended prescription lengths and 23.5% referred patients to family doctor to reduce the burden of hospital visits (Figure 4).

Response to COVID-19

Patients were routinely assessed for fever via phone before the appointment or upon arrival to the hospital (60.2%), and other COVID-19 symptoms were regularly checked (50.0%). During the hospital visit, increase of wearing gloves and mask were 54.1%, and increase of surfaces rigorously cleaning was 54.1%. Over 78% of respondents indicated face masks were required for patients. During the greatest month of COVID-19 impact, 78.6% doctors reported spending between 1-25% of their time on COVID-19 patient care. For the month before the survey, 74.5% doctors reported still spending a similar amount of time on COVID-19 patient care. The most common activities requiring their involvement included SARS-CoV-2 testing (51.5%) and COVID-19 vaccination (61.2%). The response to COVID-19 is shown in supplementary figure 1.

Potential benefits of the COVID-19 response to hepatitis elimination

Clinicians reported that despite the setbacks from the COVID-19 pandemic, potential benefits to hepatitis elimination efforts in the long-run could include overall strengthening infectious disease control (45.9%), raising awareness of medical institution with infectious disease epidemic (44.4%), including improved training of primary care professionals in infectious disease testing and management (35.7%) and improved referral network (29.1%). (Table 3)

Comparison to results from global survey

In comparison with the global survey, decreases in HBV and HCV treatment were significantly lower in Japan (HBV:32.7% vs 52.4%, p-value=0.0009; HCV: 41.8% vs 66.0%, p-value <0.0001). In addition, the number of clinicians deferring HCV screening and confirmatory laboratory testing was significantly lower in Japan compared to the global survey (51% vs 70.9%, p-value 0.0010: 68.4% vs 50.5%, p-value 0.0024). In contrast, challenges to resuming services to pre-COVID-19 levels, such as anxiety and fear, limited staff, loss of staff to COVID-19 activities, loss of space and funds were all more commonly reported challenges in our survey than the global survey (67.4% vs 37.9%, p-value <0.0001; 46.4% vs 17.5%, p-value <0.0001; 49.0% vs 6.8%, p-value <0.0001; 34.7% vs 19.4%; p-value 0.0059; 16.3% vs 6.8%, p-value 0.0201). Compared to respondents globally, respondents in Japan reported after COVID-19 infection spread about masking of staff and clinician increased 54.1% vs 82.5% (p-value < 0.0001) and for patients of masking increased was 78.6% and 55.3% (p-value < 0.0001). As for perceived benefits of COVID-19 for hepatitis elimination, expanded laboratory testing platforms was less commonly reported in Japan than in the global survey (17.9% vs 41.8%, p-value <0.0001). Other comparisons were shown on table 3.

For the greatest month of COVID-19 impact in Japan, 57.1% of clinicians used

telemedicine for treating between 1-25% patients, while for the global survey the proportion was 29.2% of clinicians. Similar comparison was noted for the month before the survey completion (p-value <0.0001). Rest result has shown on Figure 5.

During the greatest month of COVID-19 impact, most clinicians indicated that either 1-25% or 26-50% of patients were deferred for clinic or hospital visits in Japan while in the global survey, most respondents reported deferring more than 26-50%. In the month before survey completion, higher portions of clinicians reported deferring between 1-25% of hospital visits in Japan whereas in for the global survey the majority of clinicians reported deferring between 26-50% of hospital visits. (Supplementary figure 2)

Discussion

This study is the first to assess the impact of COVID-19 on hepatitis services in Japan. Members of JSH belonged to different professions, institutions and positions related to liver diseases but in our analysis, we have included the responses of medical doctors (hepatologists). COVID-19 infection severity varied by region and prefecture in Japan. However, we haven't found any significant differences of COVID-19 impact on hepatitis related services among responded 35 prefectures

Although no major supply chain disruptions related to hepatitis were noted, most of the clinician reported a decrease of 1-25% in HBV and HCV screening and confirmatory testing. Anxiety and fear among patients and lack of staff were given as contributors to the declines of screening and testing volumes. Among all services related with HBV and HCV, decline on screening, confirmatory testing, monitoring declines were reported higher than treatment. A similar trend of higher decline in screening and testing higher than treatment and monitoring had been noticed on HCC in our survey. It indicates that

Accepted Article

the patients who met diagnosis were given treatment according to the results. Besides of global survey, the trend of decreases in hepatitis-related services during COVID-19 was found similar to other studies conducted in the Netherlands for diagnosis (20), Ontario (Canada) for HBV and HCV testing. (21) However, the decline of any kind of services related to HBV and HCV might hamper to meet the set elimination goal.(2, 9, 18, 19, 22) As from the participated hepatologists impression, screening and confirmatory testing were observed highly affected than other services in COVID-19 pandemic, our results recommend for further study to evaluate the impact of COVID-19 on HBV and HCV health screening facilities.

Telemedicine was commonly used in developed countries like Japan from pre-pandemic(27) which has adopted more during COVID-19 pandemic.(28) However, beyond telemedicine, clinicians also adopted strategies including extension of prescription lengths and referral to primary care physicians. It was a positive sign and could be used in other pandemic or crisis time in the future.

In our survey, clinician reported as a part of changes on COVID-19, for staffs wearing masks were less than other countries from the global survey result. Prior COVID-19 outbreak, mask wearing was common for the medical care staff in Japan. Thus, the percentage of change was much low compared to the other countries. However, 40.8% of clinicians in our survey reported on wearing face shields regularly during patients encounter which was remarkable.

In our survey, clinicians reported time spent caring for COVID-19 patients was similar in the greatest impact month and the month prior to the survey. The probable reason was fifth wave that was ongoing during the survey period.(29)

In comparison to results of the global survey, the situation in Japan was better than in

other countries in terms of impact on screening and treatment. The most reported challenges to resuming care to pre-COVID-19 levels were limited availability of staff and loss of staff to the COVID-19 response in Japan, but the top responses differed in the global survey. A possible reason might be that 61.2% of respondents were engaged in COVID-19 vaccination but during the global survey, COVID-19 vaccination has not yet been rolled out.

HBV and HCV are substantial public health problems with high mortality and morbidity rates that will require continuous and relentless dedication to reach goals for elimination.(1, 2, 11) COVID-19 has impacted funding and health care systems across the world.(16, 17, 30, 31) The impact of the pandemic on services and interventions for chronic disease must be intensively assessed given their high morbidity and mortality. This study points to new gaps and challenges for long-running services for HBV and HCV because of the pandemic, such as declines in HBV and HCV screening and confirmatory testing whereas treatment and monitoring were not as much affected. That suggests most of the patients who were diagnosed could access treatment and monitoring during the pandemic and clinicians continued to prioritize providing care to these patients. This trend indicates in Japan once a patient is connected to a hospital or institution for treatment purposes are less likely to lose to follow up. This trend could be adopted and utilized by clinicians to connect and link the patients with hepatitis screening and confirmatory testing to the treatment directly after COVID-19 pandemic. In addition, a possible reason for a greater drop-off in screening and confirmatory testing could be anxiety and fear of COVID-19 and loss of staff to the COVID-19 response. This situation is alarming because unscreened asymptomatic carriers would remain undiagnosed and untreated and could progress to liver cirrhosis, HCC, or even death. Declines in screening, confirmatory

testing, and diagnosis could hinder the progress of HBV and HCV elimination in Japan. This information must inform efforts by policymakers and related authorities to develop actions to address this issue. Additionally, deferring of HCC screening may hinder the early detection of cancer and increase additional burden of cancer.

There were several limitations to this study and interpretation of results. First, among 47 prefectures nationwide, respondents were only from 35 prefectures with a smaller number of hepatologist responses. Secondly, on several aspects such as clinic visits deferred, volume of patients' reductions, medical doctors may have provided their impression of the experience at their institutions which may not have been verified. Thirdly, since the survey time period and stage of the pandemic was not the same for the Japan survey and the global survey, comparisons may have been biased.

Conclusion

The level of decline on hepatitis related services in Japan were lower than other countries. However, in Japan, substantial greatest declines were reported in HBV and HCV screening and confirmatory testing than for treatment initiation. Immediate action is needed to return HBV and HCV screening and confirmatory testing back to pre-pandemic levels. To do so the anxiety and fear among patients of COVID-19 infection and the loss of health care staff and facilities redirected to the COVID-19 response must be overcome. In addition, efforts should be made to leverage possible benefits of the COVID-19 response to the national hepatitis program, including improved training of clinicians in infectious disease testing and management and raising awareness of medical institution to deal with infectious disease epidemic. To achieve HBV and HCV elimination by 2030, Japan must rebound from the setbacks caused by the COVID-19 pandemic.

Abbreviations

WHO- World Health Organization, HBV- Hepatitis B Virus, HCV-Hepatitis C Virus, COVID-19 Coronavirus disease 2019, SARS-CoV-2- severe acute respiratory syndrome coronavirus2, JSH- Japan Society of Hepatology, HCC- Hepatocellular carcinoma

Acknowledgements

To the Japan Society of Hepatology (JSH) and all the medical doctors from JSH who have participated in the survey.

Number of figures and tables: 5 Figures, 3 Tables

Conflict of interest statement: The authors declare no conflicts of interest that pertain to this work.

Financial support statement:

This research was partly supported by a grant from the Japan Ministry of Health, Labour and Welfare (19HC1001)

Authors contributions:

Study concept and design: JT. Acquisition of data: MR, LH, AS, SK, TK and JT. Data management: MR, LH, AS and JT. Data analysis: MR, LH, AS and JT. Statistical analysis: MR, LH, BE, TA and JT. Interpretation of data: MR, LH, AS and JT. Manuscript development: MR, LH, AS, SO, BE, KK, TA, AR, TK, SK, JW and JT. Study supervision: JW, JT. All authors reviewed and approved the final version of the manuscript.

References

1. World Health Organization. Global health sectors strategy on Viral Hepatitis 2016-2021. June 2016.
2. World Health Organization. Global Hepatitis Report, 2017. Geneva; 2017 21 April.
3. Tanaka J, Akita T, Ko K, Miura Y, Satake M. Countermeasures against viral hepatitis B and C in Japan: An epidemiological point of view. *Hepatology research : the official journal of the Japan Society of Hepatology*. 2019;49(9):990-1002.
4. Ministry of Health LaW, Japan. Basic act on Hepatitis measure. 2011.
5. Kanto T. Messages from Japan policy for viral hepatitis. *Global health & medicine*. 2021;3(5):249-52.
6. Tanaka J, Akita T, Ohisa M, Sakamune K, Ko K, Uchida S, et al. Trends in the total numbers of HBV and HCV carriers in Japan from 2000 to 2011. *Journal of viral hepatitis*. 2018;25(4):363-72.
7. Takeuchi Y, Ohara M, Kanto T. Nationwide awareness-raising program for viral hepatitis in Japan: the "Shitte kan-en" project. *Global health & medicine*. 2021;3(5):301-7.
8. Ministry of Health LaW, Japan. Basic Guidelines for Promotion of Control Measures for Hepatitis. . 2016.
9. Tanaka J, Kurisu A, Ohara M, Ouoba S, Ohisa M, Sugiyama A, et al. Burden of chronic hepatitis B and C infections in 2015 and future trends in Japan: A simulation study. *The Lancet Regional Health – Western Pacific*.
10. Ko K, Akita T, Satake M, Tanaka J. Epidemiology of viral hepatitis C: Road to elimination in Japan. *Global health & medicine*. 2021;3(5):262-9.
11. Collaborators. PO. The case for simplifying and using absolute targets for viral hepatitis elimination goals. *Journal of viral hepatitis*. January 2021;28(1):12-9.
12. Center for Infectious Disease Research and Policy (CIDRAP) UoM. Chinese officials probe unidentified pneumonia outbreak in Wuhan: Center for Infectious Disease Research and Policy, University of Minnesota.; 2019 [Available from: <https://www.cidrap.umn.edu/news-perspective/2019/12/news-scan-dec-31-2019>].
13. (WHO) WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [updated 11 March. Available from: <https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>].
14. WHO. Novel Coronavirus (2019-nCoV) SITUATION REPORT - 1. 2021 21 January.
15. Blumenthal D, Fowler EJ, Abrams M, Collins SR. Covid-19 - Implications for the Health Care System. *N Engl J Med*. 2020;383(15):1483-8.
16. Poudel AN, Zhu S, Cooper N, Roderick P, Alwan N, Tarrant C, et al. Impact of Covid-19 on health-related quality of life of patients: A structured review. *PloS one*. 2021;16(10):e0259164.
17. Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, et al. Impact of COVID-

19 pandemic on utilisation of healthcare services: a systematic review. *BMJ Open*. 2021;11(3):e045343.

18. Pley CM, McNaughton AL, Matthews PC, Lourenço J. The global impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of hepatitis B virus (HBV) infection. *BMJ Global Health*. 2021;6(1):e004275.

19. Blach S, Kondili LA, Aghemo A, Cai Z, Dugan E, Estes C, et al. Impact of COVID-19 on global HCV elimination efforts. *Journal of hepatology*. 2021;74(1):31-6.

20. Sonneveld MJ, Veldhuijzen IK, van de Laar TJW, Op de Coul ELM, van der Meer AJ. Decrease in viral hepatitis diagnoses during the COVID-19 pandemic in the Netherlands. *Journal of hepatology*. 2021.

21. Mandel E, Peci A, Cronin K, Capraru CI, Shah H, Janssen HLA, et al. The impact of the first, second and third waves of covid-19 on hepatitis B and C testing in Ontario, Canada. *Journal of viral hepatitis*. 2022;29(3):205-8.

22. Laury J, Hiebert L, Ward JW. Impact of COVID-19 Response on Hepatitis Prevention Care and Treatment: Results From Global Survey of Providers and Program Managers. *Clinical liver disease*. 2021;17(1):41-6.

23. Kondo R, Kawaguchi N, McConnell MJ, Sonzogni A, Licini L, Valle C, et al. Pathological characteristics of liver sinusoidal thrombosis in COVID-19 patients: A series of 43 cases. *Hepatology research : the official journal of the Japan Society of Hepatology*. 2021;51(9):1000-6.

24. Kudo M, Kurosaki M, Ikeda M, Aikata H, Hiraoka A, Torimura T, et al. Treatment of hepatocellular carcinoma during the COVID-19 outbreak: The Working Group report of JAMTT-HCC. *Hepatology research : the official journal of the Japan Society of Hepatology*. 2020;50(9):1004-14.

25. Suda G, Ogawa K, Kimura M, Maehara O, Kitagataya T, Ohara M, et al. Time-dependent changes in the seroprevalence of COVID-19 in asymptomatic liver disease outpatients in an area in Japan undergoing a second wave of COVID-19. *Hepatology research : the official journal of the Japan Society of Hepatology*. 2020;50(10):1196-200.

26. Tsutsumi T, Saito M, Nagai H, Yamamoto S, Ikeuchi K, Lim LA, et al. Association of coagulopathy with liver dysfunction in patients with COVID-19. *Hepatology research : the official journal of the Japan Society of Hepatology*. 2021;51(2):227-32.

27. Ito J, Edirippulige S, Aono T, Armfield NR. The use of telemedicine for delivering healthcare in Japan: Systematic review of literature published in Japanese and English languages. *Journal of telemedicine and telecare*. 2017;23(10):828-34.

28. Golinelli D, Boetto E, Carullo G, Nuzzolese AG, Landini MP, Fantini MP. Adoption of Digital Technologies in Health Care During the COVID-19 Pandemic: Systematic Review of Early Scientific Literature. *Journal of medical Internet research*. 2020;22(11):e22280.

29. Ministry of Health LaW, Japan. COVID-19 situation in Japan 2022 [Available from: https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou_00006.html].

30. FOUNDATION MI. COVID-19 in Africa, one year on: Impact and Prospect. Angola;

2021.

31. Waheed Y. Progress on global hepatitis elimination targets. World journal of gastroenterology. 2021;27(47):8199-200.

Table 1: Affiliated facility/institution types of participated medical doctors from JSH

Participant's Affiliation	N	%
Public Hospital	54	27.6%
Clinic	7	3.6%
University Hospital	103	52.6%
Private Hospital	28	14.3%
Government Agency	2	1.0%
Others	2	1.0%
Total	196	100%

Table 2: Medical doctors from JSH responded about deferring different services during COVID-19

N=196

Aspects	During COVID-19 Service Deferred	Yes	No	N/A	No Answer
Diagnosis related	Imaging*	65.8%	29.6%	4.6%	0%
	Lab testing	68.4%	27.6%	4.1%	0%
	HCC screening	55.1%	39.8%	4.6%	0.5%
	Liver biopsy	43.4%	42.9%	13.3%	0.5%
	Gastrointestinal endoscopy	87.2%	8.7%	3.1%	1%
Public awareness and lectures related	Nutritional guidance	38.8%	49%	12.2%	0%
	Liver disease related lecture for patients	55.6%	10.7%	33.2%	0.5%
	Enlightenment activities by public lectures	55.6%	27.9%	26%	0.5%
Hospital visits related	Referral for viral hepatitis from other departments	33.7%	54.6%	11.2%	0.5%
	Extend the interval between hospital visits	65%	28.6%	6.1%	0%
	Extend the prescription interval	51%	40.3%	6.1%	2.6%

***Imaging includes all kind of diagnosis of liver diseases including HCC**

Table 3: Comparison of Japan Survey and global survey

			N=196	N=103	
Area	Aspect	Facility/issue	Japan Survey	†Global Survey	P-Value
Hepatitis related services	Screening	Decrease reported any level of HBV screening	51%	56.3%	0.3834
		Decrease reported any level of HCV screening	51%	70.9%	0.0010
	Treatment	Decrease reported any level of HBV treatment	32.7%	52.4%	0.0009
		Decrease reported any level of HCV treatment	41.8%	66.0%	<0.0001
	Testing	Lab testing deferred	68.4%	50.5%	0.0024
		Imaging deferred	65.8%	60.2%	0.3362
Mitigation strategies and challenges	Challenges to resume services as pre-COVID-19 level	Patient fear/anxiety	67.4%	37.9%	<0.0001
		Limited staff	46.4%	17.5%	<0.0001
		Loss of staff	49.0%	6.8%	<0.0001
		Inadequate PPE	12.2%	13.6%	0.7396
		Loss of space	34.7%	19.4%	0.0059
		Loss of funding	16.3%	6.8%	0.0201
		Supply shortage	13.8%	7.8%	0.1246
Response to COVID-19	Changes on infection control	Staff masks	54.1%	82.5%	<0.0001
		Patient masks	78.6%	55.3%	<0.0001
		Rigorous cleaning	54.1%	50.5%	0.5539
		Spacing patient visits	30.6%	45.6%	0.0100
		Patients checked for COVID-19 symptoms	60.2%	47.6%	0.0366
Potential benefits of COVID-19	Perceived benefits of COVID-19 on hepatitis	Increase lab testing platforms	17.9%	41.8%	<0.0001
		Improved training	35.7%	42.7%	0.2360
		Improved referral network	29.1%	22.3%	0.2101
		Improve contact tracing	13.8%	25.2%	0.0136
		Improved surveillance	14.3%	24.3%	0.0317
		Improved reporting	19.9%	18.5%	0.7630

Japan survey on medical doctors from 24 August 2021 to 03 October 2021

†Global survey on medical doctors from 12 August 2020 to 16 December 2020(22)

Figure Legends

Figure 1: Designed questionnaire to assess the impact and response of COVID-19 on HBV and HCV

This figure shows the addressed areas of our cross-sectional questionnaire survey and key points of the questionnaire. The questionnaire was similar with global survey but on highlighted (†) sections some questions were erased and added on Japan perspective.

HBV- Hepatitis B Virus, HCV-Hepatitis C Virus, COVID-19 Coronavirus disease 2019

Figure 2: Participants distribution by prefecture

This figure represents distribution of 196 medical doctors from JSH by prefecture of Japan. Grey color prefectures represent of participation of no participants, yellow color prefectures represent participants of 1-10 participants and orange color prefectures represent participation of >10 participants.

Figure 3: COVID-19 impact on HBV and HCV related screening, testing and treatment in Japan

This figure shows responses of JSH medical doctors on the level of decline on HBV and HCV screening, testing and treatment comparing with a typical month pre-COVID to the month with the most substantive change during the epidemic (in number persons of initiation).

HBV- Hepatitis B Virus, HCV-Hepatitis C Virus, SVR 12- sustained virologic response 12, COVID-19 Coronavirus disease 2019

Figure 4: Telemedicine and other adopted strategies during COVID-19 pandemic

On this figure, telemedicine and other strategies which were adopted by JSH medical doctors beside telemedicine. On both cases, the participants (JSH medical doctors) were allowed to select multiple options on telemedicine and beside telemedicine.

JSH- Japan Society of Hepatology, COVID-19- Coronavirus disease 2019

Figure 5: Comparison of telemedicine usage from Japan survey and global survey

This figure shows the comparison of using telemedicine on greatest impact month in Japan and globally. The volume of patient's percentage was responded doctors' impression on their institution. P-value were <0.0001 and significant.

List of Supporting Information

1. Supplementary Figure 1: Clinician's responses on COVID-19 in Japan

On this figure, it is shown that the participants (JSH medical doctors) responses on COVID-19. On three sections of that figure, first section is showing the changes and activities were adopted by them and staffs to control infection for the patients. On second section, it is illustrated the amount of time those doctors spent for caring COVID-19 related activities. And third section, the role or activities specifically related to COVID-19 possible care.

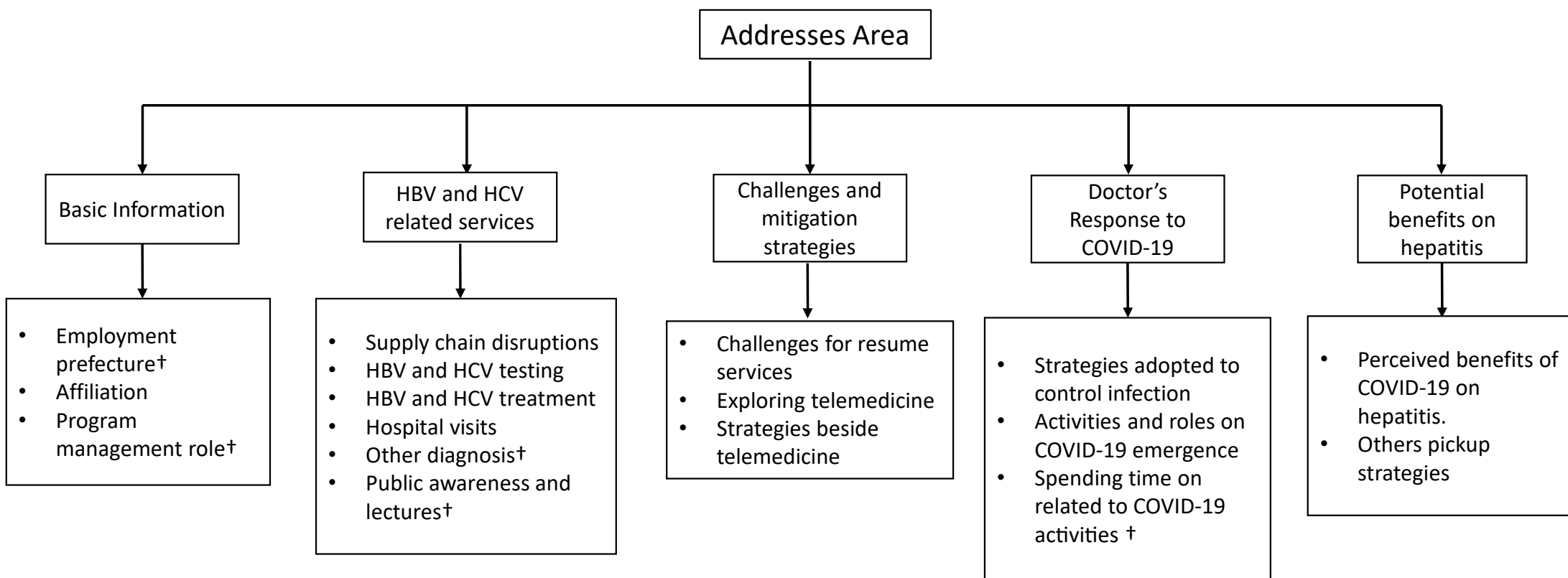
2. Supplementary Figure 2: Hospital or clinic visit deferred due to COVID-19

in a) greatest month of COVID-19 impact, b) past month of survey

This figure shows the percentage of hospital visit deferred in prefecture wise in Japan and country wise in global survey. The responses were for greatest impact month of COVID-19 and the status of past month of survey. The red dot and blue dot are showing the most frequent answer of that certain prefecture or country.

3. Supplementary table 1: Questionnaire

Figure 1: Designed questionnaire to assess the impact and response of COVID-19 on HBV and HCV



†On this section several questions added with global survey questionnaire

Figure 2: Participants distribution by prefecture

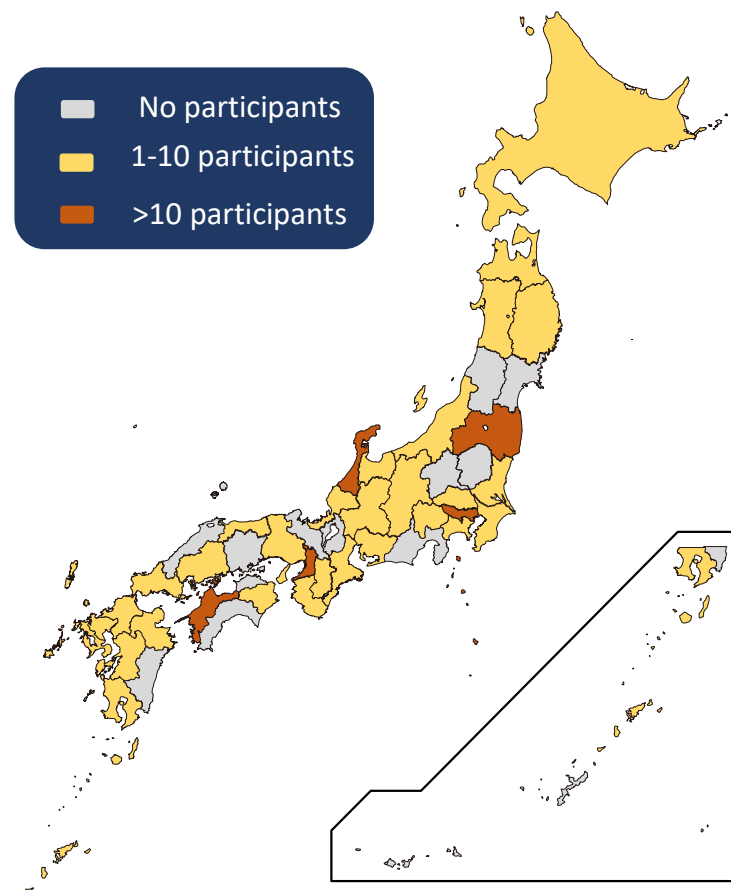


Figure 3: COVID-19 impact on HBV and HCV related screening, testing and treatment

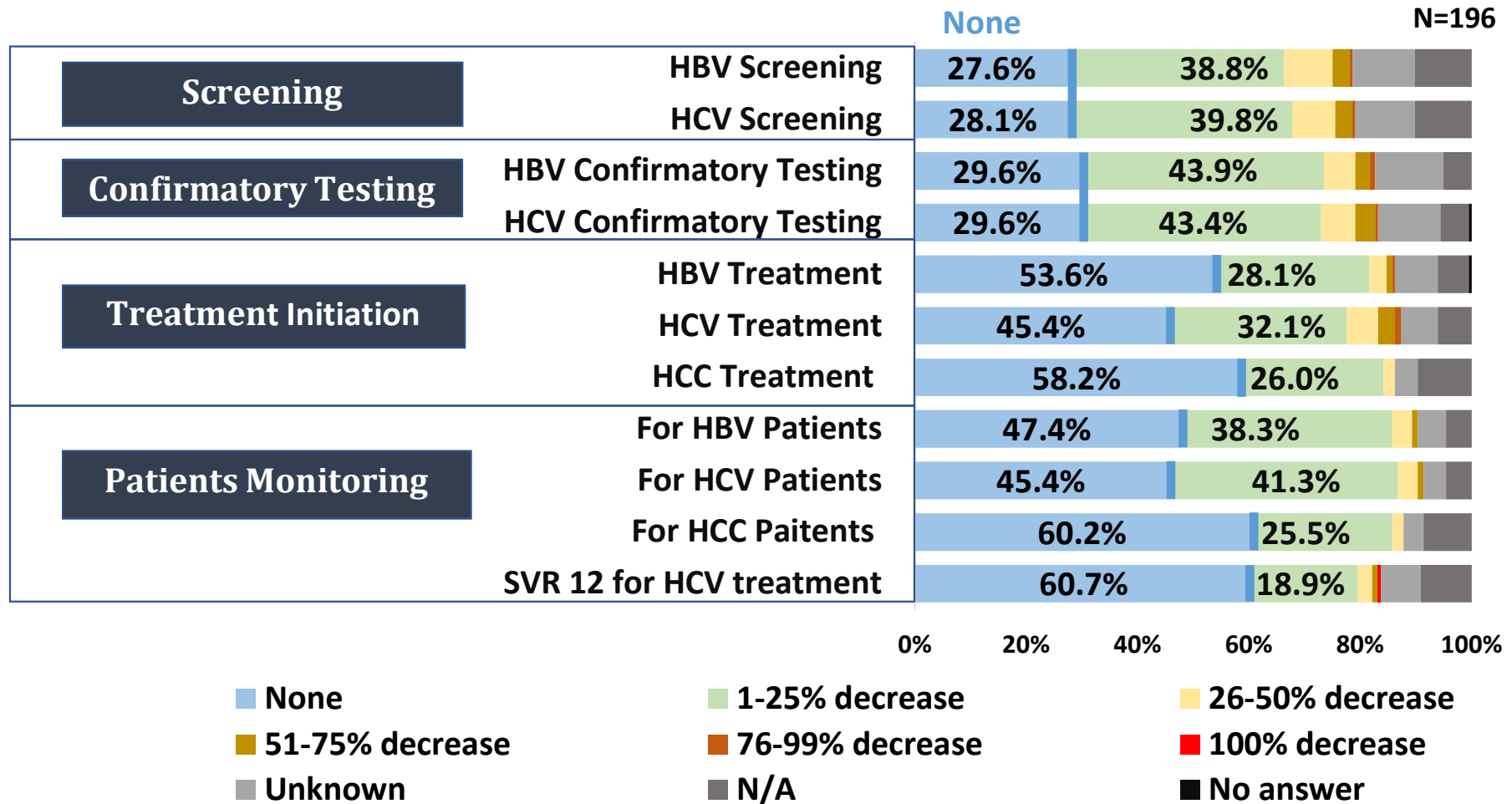
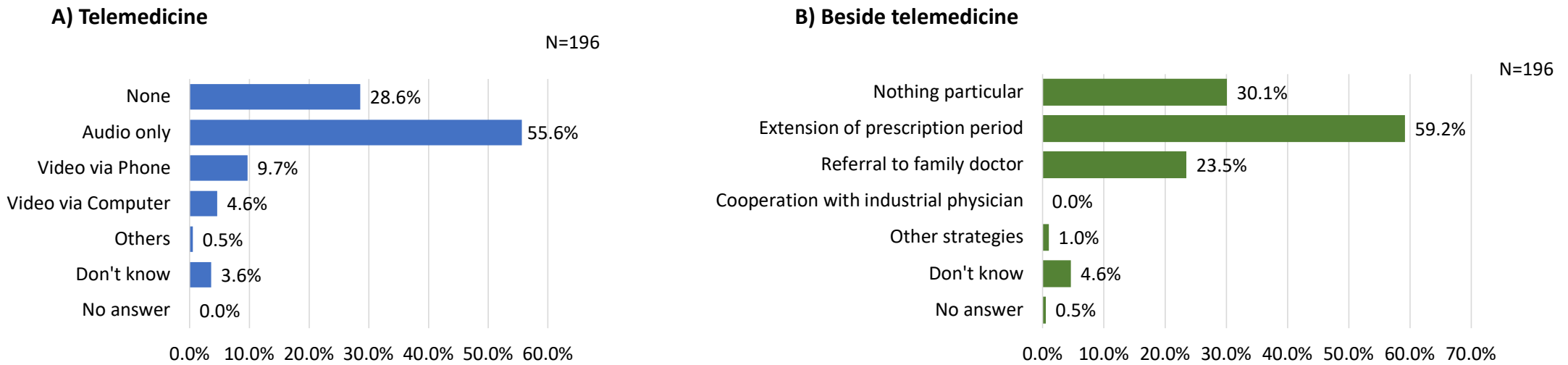


Figure 4: Adopted mitigation strategies during COVID-19



*Medical doctors selected multiple options on both cases

Figure 5: Comparison of the percentage of using telemedicine from Japan survey and global survey

*At the time of the greatest impact Month of COVID-19

