—Original—

Pre-Vaccination Anti-Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Seroprevalence in Workers at Three Japanese Hospitals

Yoko Takayama[1,2], Toshiaki Komatsu[3], Tatsuhiko Wada[4], Shin Nihonyanagi[2], Takayuki Hoshiyama[2,4], Tatsumi Moriya[5], Shizue Shimamura[6], Naoko Kajigaya[7], Masanori Naito[8], Osamu Takeuchi[9], Yuki Bando[7,10], Masahiko Watanabe[11], Masatsugu Iwamura[12] and Hideaki Hanaki[13]

[1]Department of Infection Control and Infectious Diseases, Research and Development Center for New Medical Frontiers, Kitasato University School of Medicine, Kanagawa, Japan
[2]Department of Infection Control and Prevention, Kitasato University Hospital, Kanagawa, Japan
[3]Department of Pharmacy, Kitasato University Hospital, Kanagawa, Japan
[4]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan
[5]Kitasato University Health Care Center, Kanagawa, Japan
[6]Department of Clinical Trial Center, Kitasato University Medical Center, Saitama, Japan
[7]Department of Infection Control and Prevention, Kitasato University Medical Center, Saitama, Japan
[8]Department of Gastroenterological and General Surgery, St. Marianna University School of Medicine, Kanagawa, Japan
[9]Biomedical Laboratory, Department of Research, Kitasato University Kitasato Institute Hospital, Tokyo, Japan
[10]Department of Pediatrics, Kitasato University Medical Center, Saitama, Japan
[11]Department of Surgery, Kitasato University Kitasato Institute Hospital, Tokyo, Japan
[12]Department of Urology, Kitasato University School of Medicine, Kanagawa, Japan
[13]Infection Control Research Center, The Omura Satoshi Memorial Institution, Kitasato University, Tokyo, Japan

Background: Antibody testing is essential for accurately estimating the number of people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study aimed to investigate the influence of background factors on seroprevalence by testing for anti-SARS-CoV-2 antibodies in blood samples obtained from the staff of three hospitals.
Methods: This cross-sectional observational study was conducted from June 8 to July 4, 2020, as part of a mandatory health examination. Leftover blood samples collected during the health examinations at each hospital were used to test for the presence of anti-SARS-CoV-2 antibodies. The Elecsys Anti-SARS-CoV-2 RUO assay was used for antibody detection. The relationship between staff age, gender, body mass index, blood pressure, work environments with different exposure risks, place of residence, and campus location and seroprevalence was investigated. The data were anonymized prior to analysis.
Results: A total of 3,677 individuals were included in the study, comprising 2,554 females (69.5%) and 1,123 males (30.5%). Anti-SARS-CoV-2 antibody (immunoglobulin G) was detected in 13 participants (0.35%). Seroprevalence was slightly higher in males than females (0.62% vs. 0.23%, P=0.08). By occupation, anti-SARS-CoV-2 antibodies were found in 6 (0.75%) physicians, 6 (0.31%) nurses, and one individual (0.11%) in the medical personnel group, with slightly higher levels in physicians. No significant difference was noted in the seroprevalence in terms of all background factors.
Conclusions: Our study shows that the background factors do not impact seropositivity rates. Thorough daily infection control and adherence to recommended health guidelines were found to reduce infection risk. (J Nippon Med Sch 2022; 89: 513–519)

Key words: anti-severe acute respiratory syndrome coronavirus 2 antibody, seroprevalence, coronavirus disease, university hospitals, healthcare workers

Introduction

Coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first reported in China in December 2019, has

Correspondence to Yoko Takayama, Department of Infection Control and Infectious Diseases, Research and Development Center for New Medical Frontiers, Kitasato University School of Medicine, 1–15–1 Kitasato, Minami-ku, Sagamihara-shi, Kanagawa 252–0374, Japan
E-mail: yoko@med.kitasato-u.ac.jp
https://doi.org/10.1272/jnms.JNMS.2022_89-511
Journal Website (https://www.nms.ac.jp/sh/jnms/)

resulted in >281 million cases and >5.4 million deaths worldwide (as of December 29, 2021)[1].

Healthcare workers (HCWs) are a high-risk group for SARS-CoV-2 infection[2,3]. Several studies have investigated the links between seroprevalence and environmental risks[4,5]. For example, studies examining the correlation between SARS-CoV-2 infection and individual behavioral history found that the risk of infection was higher in conditions with inadequate infection control measures, such as cohabitation, attending school or private gatherings, visiting bars and restaurants, and participating in indoor sports activities[4,5]. It has also been reported that the seroprevalence of SARS-CoV-2 antibodies is high among healthcare workers who have frequent contact with patients, such as nurses and support service workers[6,7]. It is clear from previous studies that various environmental risk factors can lead to increased transmission of SARS-CoV-2.

This study aimed to investigate the relationship of background factors with seroprevalence by testing for anti-SARS-CoV-2 antibodies in blood samples obtained from staff in three hospitals. The use of seroprevalence provides insights into the spread of the COVID-19 pandemic in Japan before vaccines was introduced.

Materials and Methods

Study Design and Participants

In this study, we analyzed information collected during routine staff health check-ups at three hospitals of the Kitasato Institute in Japan and tested the leftover serum samples from these routine health check-ups for the presence of anti-SARS-CoV-2 antibodies. This cross-sectional observational study was conducted at three affiliated hospitals of the Kitasato Institute located in the Tokyo metropolitan area: Minato Ward (Kitasato University Kitasato Institute Hospital [KUKIH]); Sagamihara City, Kanagawa Prefecture (Kitasato University Hospital [KUH]); and Kitamoto City, Saitama Prefecture (Kitasato Medical Center [KMC]). Health and residency data were collected as part of a mandatory employee health check-up at the three hospitals. Physical examinations were conducted at the hospitals where the staff worked. The health check-ups were conducted from June 8 to July 4, 2020. Of the 3,734 eligible employees, 3,677 (98.5%) consented to participation in this study. As the study was conducted before the availability of COVID-19 vaccines, all staff were unvaccinated. We analyzed the association between the anonymized health examination data (age, sex, body mass index, blood pressure [BP], and hospital affiliation) and area of residence (at the prefecture city ward level). Anonymized leftover serum samples collected from individuals during their health examinations at each hospital were reprocessed to test for the presence of anti-SARS-CoV-2 antibodies. Health examination information, residence information, and antibody results were consolidated, and all data analyses were performed using anonymized data. Although a small percentage of participants held positions in more than one of the three hospitals, most underwent physical examinations at their primarily affiliated hospital. KUKIH, KUH, and KMC are all tertiary care university-affiliated general hospitals. There are 329 beds at KUKIH, 1,190 at KUH, and 327 at KMC. Although the three hospitals are not medical institutions designated for infectious diseases, they accepted patients with COVID-19. We defined nurses and nursing assistants as "nurses" and laboratory technicians, pharmacists, radiology technicians, medical engineering technicians, rehabilitation staff, nutrition staff, and nursery staff as "medical personnel." According to the European Society of Cardiology and the European Society of Hypertension guidelines, hypertension was defined as BP> 140/90 mmHg[8].

Measurement of Anti-SARS-CoV-2 Antibodies

Anti-SARS-CoV-2 antibodies were measured using the Elecsys Anti-SARS-CoV-2 RUO assay (Roche Diagnostics, Basel, Switzerland), which is based on the modified double-antigen sandwich immunoassay with recombinant protein representing the nucleocapsid antigen that measures the total antibody against SARS-CoV-2 (pan-immunoglobulin). The assay was performed using a fully automated Cobas e801 analyzer (Roche Diagnostics, Basel, Switzerland). According to the U.S. Food and Drug Administration[9,10], the Elecsys anti-SARS-CoV-2 system has 100% sensitivity (≥14 days after a positive polymerase chain reaction assay) and 99.8% specificity. The results were reported as the cut-off index, and results with a cut-off index >1.0 were interpreted as positive (anti-SARS-CoV-2 antibody present). The analytical and clinical performance of the assay has been evaluated and described in a previous study[11].

Statistical Analysis

The Kolmogorov-Smirnov test was used to analyze the normality of the data. Comparisons of normally distributed variables were performed using the t-test, whereas comparisons of non-normally distributed variables were performed using the Mann-Whitney *U* test. Comparisons of categorical variables were performed using Fisher's exact test. Seroprevalence with 95% confidence intervals

Table 1 Occupations of the severe acute respiratory syndrome coronavirus 2 seroprevalence survey participants

Hospital	Sex	Physicians	Nurses[a)]	Medical personnel[b)]
KUKIH (Tokyo)	Male	19	6	26
	Female	11	110	51
KUH (Kanagawa)	Male	494	186	241
	Female	194	1,296	478
KMC (Saitama)	Male	60	22	69
	Female	19	326	69
Total		797	1,946	934

[a)] Including nursing assistants
[b)] Includes laboratory technicians, pharmacists, radiology technicians, medical engineering technicians, rehabilitation staff, nutrition staff, and nursery staff
KUKIH: Kitasato University Kitasato Institute Hospital, KUH: Kitasato University Hospital, KMC: Kitasato Medical Center

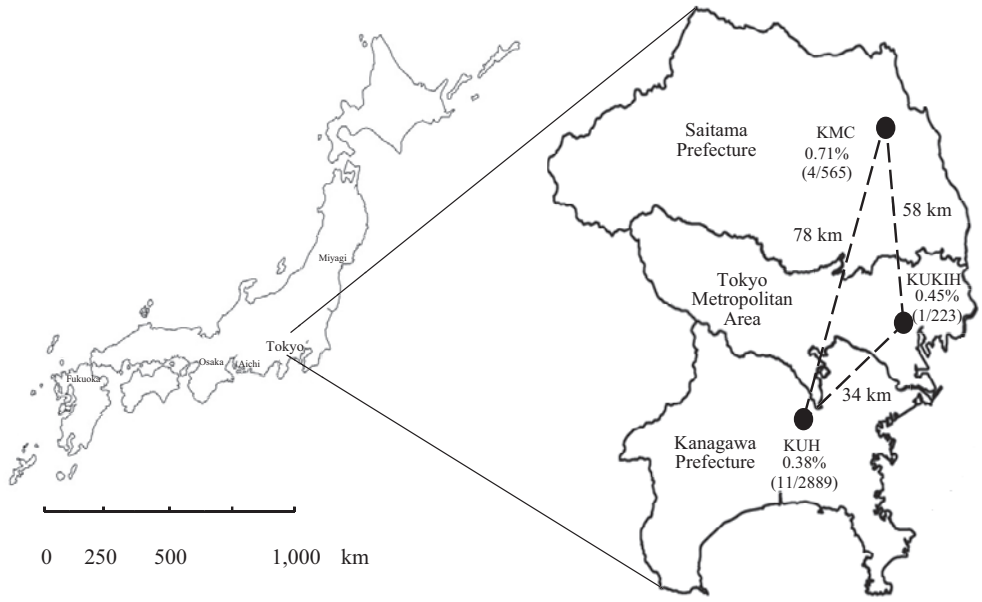

Fig. 1 Location and seroprevalence of anti-severe acute respiratory syndrome coronavirus 2 antibodies among the three hospitals
Tokyo, Kanagawa, and Saitama cover an area of approximately 8,405 km^2.
KUKIH: Kitasato University Kitasato Institute Hospital, KUH: Kitasato University Hospital, KMC: Kitasato Medical Center

(CI) was calculated using the exact binomial technique. The statistical analyses were performed using the JMP version 14.0 software (SAS Institute, Inc., Cary, NC, USA).

Ethical Approval

This study was approved by the ethics committees of KUKIH (20031), KUH (B20-127), and KMC (2020010) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

Anti-SARS-CoV-2 Antibody Prevalence

A total of 3,677 staff members (223 from KUKIH, 2,889 from KUH, and 565 from KMC) were included in the study. Of these, 2,554 (69.5%) were females and 1,123 (30.5%) were males (**Table 1**). The mean age ± standard deviation was 35 ± 11 years. The occupations of the participants are shown in **Table 1**. SARS-CoV-2-specific antibodies (immunoglobulin G) were detected in 13 individuals (0.35%). The seroprevalence according to the hospital is shown in **Figure 1**.

Table 2 Association of selected variables with seroprevalence among staff members tested for severe acute respiratory syndrome coronavirus 2 at the three affiliated hospitals

Variable		Total participants, No.	Seropositive participants		P value
			No.	% (95% CI)	
Total		3,677	13	0.35 (0.19-0.60)	
Age (years)	≤29	1,422	4	0.28 (0.08-0.72)	0.13
	30–39	1,018	1	0.10 (0.002-0.55)	
	40–49	664	5	0.75 (0.25-1.75)	
	≥50	573	3	0.52 (0.11-1.52)	
Sex	Male	1,123	7	0.62 (0.25-1.28)	0.08
	Female	2,554	6	0.23 (0.09-0.51)	
Body mass index (kg/m^2)	<30	3,575	12	0.34 (0.17-0.59)	0.31
	≥30	102	1	0.98 (0.02-5.34)	
Blood pressure (mmHg)	≤140/90	3,624	12	0.33 (0.17-0.58)	0.17
	>140/90	53	1	1.89 (0.05-10.07)	
Occupation	Physicians	797	6	0.75 (0.28-1.63)	0.09
	Nurses [a]	1,946	6	0.31 (0.11-0.67)	
	Medical personnel [b]	934	1	0.11 (0.002-0.60)	
Place of residence	Live in the 23 wards of Tokyo	521	2	0.38 (0.05-1.38)	0.71
	Live outside the 23 wards of Tokyo	3,156	13	0.35 (0.17-0.62)	
Hospital	KUKIH (Tokyo)	223	8	0.45 (0.01-2.47)	0.28
	KUH (Kanagawa)	2,889	1	0.28 (0.12-0.54)	
	KMC (Saitama)	565	4	0.71 (0.19-1.80)	

[a] Including nursing assistants

[b] Includes laboratory technicians, pharmacists, radiology technicians, medical engineering technicians, rehabilitation staff, nutrition staff, and nursery staff

CI: confidence interval, KUKIH: Kitasato University Kitasato Institute Hospital, KUH: Kitasato University Hospital, KMC: Kitasato Medical Center

Association of Seroprevalence with Selected Variables

The association between SARS-CoV-2 infection status and the selected variables is shown in **Table 2**. Seroprevalence was slightly higher in males than females (0.62% vs. 0.23%, P=0.08). By occupation, anti-SARS-CoV-2 antibodies were found in 6 (0.75%, 95% CI: 0.28-1.63) physicians, 6 (0.31%, 95% CI: 0.11-0.67) nurses, and one individual (0.11%, 95% CI: 0.002-0.60) in the medical personnel group, with slightly higher levels in physicians. The positive rate by age was 0.28% (95% CI: 0.08-0.72), 0.10% (95% CI: 0.002-0.55), 0.75% (95% CI: 0.25-1.75), and 0.52% (95% CI: 0.11-1.52) for those below 29, in their 30s, in their 40s, and over 50 years old, respectively. However, no statistically significant differences were noted across groups when tested for age, gender, BMI, BP, occupation, place of residence, and campus location.

Health Examination Data of Seropositive Staff

Table 3 shows the health examination data of the 13 staff who tested positive for the anti-SARS-CoV-2 antibody. All six doctors were male, and five of the six nurses were female. None of the staff had clinical symptoms at the time of the health examination, and there were no significant findings on white blood cell or chest X-rays. The antibody titer varied from 1-132 cut-off index (C.O.I.) with a median antibody titer of 37.3.

Discussion

Serum antibody testing is a critical tool in managing infectious diseases and is used to diagnose, evaluate herd immunity, and determine whether immunity is acquired after vaccination. Antibody measurement is important because COVID-19 symptoms are often absent to mild. We found a 0.35% seroprevalence to SARS-CoV-2 among HCWs from three medical university hospitals with intensive care units located in the southern Kanto region of Japan. The first COVID-19 emergency declaration in Japan was issued from April 7 to May 25, 2020. The Japanese government surveyed the antibody prevalence using the Elecsys Anti-SARS-CoV-2 immunoassay among residents of major Japanese cities from June 1 to June 7 and from December 14 to December 25, 2020. The area tested in June were Tokyo, Osaka, and Miyagi, with a seroprevalence of 0.30%, 0.34%, and 0.23%, respectively. The second survey in December revealed a seroprevalence of 0.91%, 0.58%, 0.14%, 0.54%, and 0.19% in Tokyo, Osaka,

Table 3 Line listing from medical examinations of healthcare workers who tested positive for anti-severe acute respiratory syndrome coronavirus 2 antibodies

Occupations	Sex	Age	Smoking status	BMI (kg/m^2)	WBC ($/mm^3$)	anti-SARS-CoV-2 antibody (C.O.I.)	Chest X-ray
Physician	Male	Thirties	Nonsmoker	25.9	4.4	54.5	None
Physician	Male	Forties	Nonsmoker	20.7	5.6	81.7	Obsolete shadows in both upper pulmonary fields
Physician	Male	Forties	Nonsmoker	26.7	6.8	54	None
Physician	Male	Forties	Nonsmoker	23.9	6.5	4.7	None
Physician	Male	Fifties	Unknown	20.7	4.3	2.2	None
Physician	Male	Seventies	Nonsmoker	18.1	6.6	1.2	Obsolete shadows in both upper pulmonary fields
Nurse [a)]	Male	Twenties	Unknown	30.5	5.4	107	None
Nurse [a)]	Female	Twenties	Nonsmoker	21.6	4.3	132	None
Nurse [a)]	Female	Twenties	Unknown	20.5	5.9	5.5	None
Nurse [a)]	Female	Twenties	Unknown	18.4	6.3	37.3	None
Nurse [a)]	Female	Forties	Unknown	22.3	4.3	121	None
Nurse [a)]	Female	Fifties	Nonsmoker	29.8	7.3	2	Funicular shadow in left inferior pulmonary area
Medical personnel	Female	Forties	Nonsmoker	18.6	4.4	1	None

[a)] Including nursing assistants, BMI: body mass index, WBC: white blood cell, C.O.I.: cut-off index

Miyagi, Aichi, and Fukuoka, respectively[12,13]. The same measurement protocol was used in this study, and the study findings are consistent with the results of the Japanese government surveys of the general population. COVID-19 is communicable even before the onset of disease symptoms, and approximately 11-33% of SARS-CoV-2 infections are asymptomatic[14,15]. A report of anti-SARS-CoV-2 antibody measurements in 3,248 HCWs from 13 hospitals in the United States reported a seroprevalence of 6%, and 69% had no history of COVID-19 diagnosis[16]. Therefore, a serological diagnostic method that detects anti-SARS-CoV-2 antibodies in the blood is essential to determine the number of cases accurately.

This study found no significant difference in the antibody seroprevalence according to background factors. The slightly higher seroprevalence in the older age group, males, and physicians could be due to the older age group of the positive physicians and the fact that the 6 of them were males. Other studies have reported that the severity of COVID-19 is higher in older patients, males, and individuals with comorbidities[17,18]. There is no evidence that hypertension is associated with an increased risk of SARS-CoV-2 infection[19]. The lower susceptibility to viral infections among females than among males may be due to the protection offered by the X chromosome and sex hormones, which play an important role in innate and adaptive immunity[20]. Although there were more females among various occupations in our study, there was no significant difference in the seroprevalence of anti-SARS-CoV-2 antibodies. Fukuda et al. classified physicians and nurses as a high-risk group for pathogen exposure and reported antibody-positive rates[21]. During the 1918-1919 influenza pandemic, nurses and physicians were intensively exposed to the pandemic A/H1N1 strain. Nursing staff who were new to their assignments at the time of the influenza pandemic were at a higher risk of influenza-related mortality because of occupational exposures to bacterial respiratory pathogens that they had not previously encountered[22]. This study was conducted in the early stage of the SARS-CoV-2 epidemic. Compared to the present, we estimate that the risk of exposure to physicians and nurses was higher because this was when the probability that a somewhat limited number of personnel, mainly physicians and nurses, response to COVID-19 patients was high. However, in this study, the seroprevalence of anti-SARS-CoV-2 antibodies was examined separately by occupation; no significant difference was observed, suggesting that the impact of contact frequency on seroprevalence was low. Large differences in the seroprevalence of anti-SARS-CoV-2 antibodies among HCWs (0.3-43%) have been reported in different studies[21,23–25], suggesting that the preva-

lence of SARS-CoV-2 infection among HCWs varies widely between countries. Furthermore, there are indications that old buildings, small spaces, and a lack of optimal facilities for isolating infectious patients may also increase the risk of infection among HCWs[26]. It has been reported that closer contact with COVID-19 individuals is associated with antibody positivity[6,7]. None of the three affiliated hospitals in this study was a nationally designated infectious disease hospital. Although the three hospitals were operated separately, a common nosocomial infection control manual was used in all three hospitals before the COVID-19 pandemic. Therefore, the same infection control measures were in place in the three study hospitals. As previously reported[27], the study results also indicate that thorough daily infection control measures and adherence to guidelines can reduce the risk of SARS-CoV-2 infection, regardless of the nature of the work and frequency of exposure.

The presence of serum antibodies is associated with a low risk of re-infection[28,29]. However, among individuals who have recovered from COVID-19, antibodies may not be sufficient to prevent reinfection, especially in individuals with mild disease[30], and there is a risk of reinfection in individuals with previous SARS-CoV-2 infection[31]. Since antibodies produced in past infections may not prevent reinfection, it is necessary to monitor the duration of the immune response by assessing the trends in serum antibody retention.

This study had some limitations. First, the relationship between the antibodies measured and the neutralizing activity against SARS-CoV-2 was not evaluated. However, immunoassays that recognize antibodies targeting different domains of the S protein have been demonstrated to correlate well with virus-neutralizing activity[32,33]. Second, multiple tests could increase the reliability of the results; however, in this study, only one method was used. Third, we did not examine the relationship between the frequency of contact with COVID-19 patients and seroprevalence. Since the study was conducted anonymously, we could not ascertain the actual number.

In our study, no significant difference was noted in the anti-SARS-CoV-2 antibody seroprevalence in terms of all background factors. Although the results were obtained from three hospitals, our findings largely reflect the prevalence of SARS-CoV-2 before vaccination in Tokyo, Kanagawa, and Saitama. This study shows that adherence to current infection prevention and control measures can reduce the risk of SARS-CoV-2 infection, regardless of the hospital location.

Acknowledgments: We would like to thank all the staff members of the Shirokane, Sagamihara, and Kitamoto campuses who were involved in this study.

Funding/Support: This work was supported by a COVID-19 countermeasures project at the Kitasato Institute, Tokyo, Japan.

Conflict of Interest: The authors do not have any conflicts of interest to declare.

References

1. WHO Coronavirus (COVID-19) dashboard. World Health Organization [Internet]. 2021 [cited 2021 Dec 29]. Available from: https://covid19.who.int/
2. Aghaizu A, Elam G, Ncube F, et al. Preventing the next 'SARS' - European healthcare workers' attitudes towards monitoring their health for the surveillance of newly emerging infections: qualitative study. BMC Public Health. 2011 Jul 8;11:541.
3. Psichogiou M, Karabinis A, Pavlopoulou ID, et al. Antibodies against SARS-CoV-2 among health care workers in a country with low burden of COVID-19. PLoS One. 2020 Dec 3;15(12):e0243025.
4. Galmiche S, Charmet T, Schaeffer L, et al. Exposures associated with SARS-CoV-2 infection in France: a nationwide online case-control study. Lancet Reg Health Eur. 2021 Aug;7:100148.
5. Kianersi S, Ludema C, Macy JT, et al. A cross-sectional analysis of demographic and behavioral risk factors of severe acute respiratory syndrome coronavirus 2 seropositivity among a sample of U.S. college students. J Adolesc Health. 2021 Aug;69(2):219–26.
6. Purswani MU, Bucciarelli J, Jose Tiburcio J, et al. SARS-CoV-2 Seroprevalence Among Healthcare Workers by Job Function and Work Location in a New York Inner-City Hospital. J Hosp Med. 2021 May;16(5):282–9.
7. Rodriguez A, Arrizabalaga-Asenjo M, Fernandez-Baca V, et al. Seroprevalence of SARS-CoV-2 antibody among healthcare workers in a university hospital in Mallorca, Spain, during the first wave of the COVID-19 pandemic. Int J Infect Dis. 2021 Apr;105:482–6.
8. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018 Oct;36(10):1953–2041.
9. Cobas: Elecsys Anti-SARS-CoV-2 - instructions for use. Cobas [Internet]. 2021 [cited 2021 Dec 2]. Available from: https://www.fda.gov/media/137605/download
10. US Food and Drug Administration. EUA Authorized Serology Test performance. FDA [Internet]. 2021 [cited 2021 Dec 2]. Available from: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance
11. Kittel M, Findeisen P, Muth MC, et al. Specificity testing by point prevalence as a simple assessment strategy using the Roche Elecsys® anti-SARS-CoV-2 immunoassay. Int J

Infect Dis. 2021 Apr;105:632−8.
12. Ministry of Health, Labour and Welfare, Japan. Kotai hoyu chosa sokuho kekka [Results of an antibody possession survey. Japan] [Internet]. 2021 [cited 2021 Dec 2]. Available from: https://www.mhlw.go.jp/content/000734482.pdf. Japanese.
13. Yoshiyama T, Saito Y, Masuda K, et al. Prevalence of SARS-CoV-2-specific antibodies, Japan, June 2020. Emerg Infect Dis. 2021 Feb;27(2):628−31.
14. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: a systematic review. Ann Intern Med. 2021 May;174(5):655−62.
15. Ge Y, Martinez L, Sun S, et al. COVID-19 transmission dynamics among close contacts of index patients with COVID-19: a population-based cohort study in Zhejiang Province, China. JAMA Intern Med. 2021 Oct 1;181(10):1343−50.
16. Self WH, Tenforde MW, Stubblefield WB, et al. Seroprevalence of SARS-CoV-2 among frontline health care personnel in a multistate hospital network - 13 academic medical centers, April-June 2020. MMWR Morb Mortal Wkly Rep. 2020 Sep 4;69(35):1221−6.
17. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507−13.
18. Rashedi J, Mahdavi Poor B, Asgharzadeh V, et al. Risk factors for COVID-19. Infez Med. 2020 Dec 1;28(4):469−74.
19. Kreutz R, Algharably EA, Azizi M, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovasc Res. 2020 Aug 1;116(10):1688−99.
20. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2019 Jun;56(3):308−21.
21. Fukuda H, Seyama K, Ito K, et al. SARS-CoV-2 seroprevalence in healthcare workers at a frontline hospital in Tokyo. Sci Rep. 2021 Apr 16;11(1):8380.
22. Shanks GD, MacKenzie A, Waller M, Brundage JF. Low but highly variable mortality among nurses and physicians during the influenza pandemic of 1918-1919. Influenza Other Respir Viruses. 2011 May;5(3):213−9.
23. Sandri MT, Azzolini E, Torri V, et al. SARS-CoV-2 serology in 4000 health care and administrative staff across seven sites in Lombardy, Italy. Sci Rep. 2021 Jun 10;11(1):12312.
24. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054−62.
25. Behrens GMN, Cossmann A, Stankov MV, et al. Perceived versus proven SARS-CoV-2-specific immune responses in health-care professionals. Infection. 2020 Aug;48(4):631−4.
26. Jespersen S, Mikkelsen S, Greve T, et al. Severe acute respiratory syndrome coronavirus 2 seroprevalence survey among 17 971 healthcare and administrative personnel at hospitals, prehospital services, and specialist practitioners in the Central Denmark Region. Clin Infect Dis. 2021 Nov 2;73(9):e2853−60.
27. Piccoli L, Ferrari P, Piumatti G, et al. Risk assessment and seroprevalence of SARS-CoV-2 infection in healthcare workers of COVID-19 and non-COVID-19 hospitals in Southern Switzerland. Lancet Reg Health Eur. 2021 Feb 1;100013.
28. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody status and incidence of SARS-CoV-2 infection in health care workers. N Engl J Med. 2021 Feb 11;384(6):533−40.
29. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection rates among patients who previously tested positive for coronavirus disease 2019: a retrospective cohort study. Clin Infect Dis. 2021 Nov 16;73(10):1882−6.
30. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild Covid-19. N Engl J Med. 2020 Sep 10;383(11):1085−7.
31. Letizia AG, Ge Y, Vangeti S, et al. SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study. Lancet Respir Med. 2021 Jul;9(7):712−20.
32. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends Immunol. 2020 May;41(5):355−9.
33. Padoan A, Bonfante F, Sciacovelli L, Cosma C, Basso D, Plebani M. Evaluation of an ELISA for SARS-CoV-2 antibody testing: clinical performances and correlation with plaque reduction neutralization titer. Clin Chem Lab Med. 2020 Oct 25;58(11):e247−9.

(Received, January 2, 2022)
(Accepted, April 13, 2022)
(J-STAGE Advance Publication, May 30, 2022)