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Hospital-wide antigen screening for coronavirus disease in a tertiary reference center in Sapporo, Japan

A single-center observational study

Yoshinosuke Shimamura, MPH*[iD], Hiroki Komazawa, PharmD, Junko Oikawa, PhD, Yasushi Furuta, PhD

Abstract

Hospital-wide screenings for coronavirus disease (COVID-19) are important to identify healthcare workers at risk of exposure. However, the currently available diagnostic tests are expensive or only identify past infection. Therefore, this single-center observational study aimed to assess the positivity rate of hospital-wide antigen screening tests for COVID-19 and evaluate clinical factors associated with antigen positivity during a COVID-19 institutional outbreak in Sapporo, Japan.

We analyzed the data of 1615 employees who underwent salivary or nasal swab antigen tests on November 18, 2020, to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Laboratory confirmation using reverse transcriptase polymerase chain reaction was performed for those with positive viral serology. The demographic characteristics, job titles, and risk of contact with COVID-19 patients were compared between employees with and without COVID-19.

A total of 19 employees (1.2%) tested positive for the SARS-CoV-2 antigen. The positivity rate was high among rehabilitation therapists (2.1%) and employees in the low-risk contact group (6.1%). Although there was no association between the job titles and the seropositivity rate, those in the low-risk contact group had an increased risk of testing positive for the viral antigen (odds ratio, 8.67; 95% confidence interval, 3.30–22.8).

The antigen positivity rate was low during the hospital outbreak, suggesting that risk assessment of exposure to COVID-19 patients may provide more useful information than using job titles to identify infected health care providers.

Abbreviations: CI = confidence interval, COVID-19 = coronavirus disease, IgG = immunoglobulin G, OR = odds ratio, PPE = personal protective equipment, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: antigen, Coronavirus disease, Japan

1. Introduction

Coronavirus disease (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a global pandemic.[1–3] Several molecular factors are involved in the pathogenesis of COVID-19, including angiotensin converting enzyme 2 cell receptor for host cell entry, 3-chymotrypsin-like protease for the processing of viral proteins, and RNA-dependent RNA polymerase for the viral replication. This knowledge can be utilized in drug-repurposing analysis to find suitable drug candidates. Interestingly, a previous study using an *in-silico* analysis reported that quinoline-based SARS-CoV-2, 3-chymotrypsin-like protease, and RNA-dependent RNA polymerase inhibitors could be potential inhibitors for SARS-CoV-2 infection.[4]

A surge in the number of COVID-19 patients has a large impact on local communities and healthcare systems. As the pandemic progresses, the number of studies reporting outbreaks of COVID-19 in medical facilities is increasing worldwide.[5–11] Hospital-wide screening tests are needed to identify health care workers and hospitalized patients who may have undiagnosed COVID-19 in nosocomial COVID-19 outbreaks.[5–7] Reverse transcriptase polymerase chain reaction (RT-PCR) is presently the criterion standard for diagnosing COVID-19;

however, other diagnostic tests, including antibody tests and antigen testing, can be used.[12,13] Previous studies in Europe have reported that SARS-CoV-2 immunoglobulin G (IgG) antibodies were detected in 1.6% to 6.0% of health care workers.[8–10] Antigen testing can also be an alternative initial test, given its high specificity, simple technical process, and low cost.[14,15] To the best of our knowledge, investigations of nosocomial COVID-19 outbreaks using antigen testing for SARS-CoV-2 have not yet been reported in the literature.

Therefore, we aimed to investigate the positivity rate of antigen testing for SARS-CoV-2 among hospital employees and explore clinical factors associated with antigen positivity at a tertiary care institution in Sapporo, Japan, during the COVID-19 institutional outbreak in November 2020.

2. Methods

2.1. Study design and participants

This was a single-center, observational study conducted from November 18, 2020, to December 4, 2020, at the Teine Keijinkai Medical Center, which is a 670-bed tertiary medical center in Sapporo, Hokkaido, Japan. We included a total of 1615 employees of the Teine Keijinkai Medical Center who were screened for COVID-19 using SARS-CoV-2 antigen testing of salivary or nasal swab specimens (FUJIREBIO Inc, Tokyo, Japan) according to the manufacturer's instructions.[16,17] Employees who were tested with RT-PCR during the nosocomial outbreak were excluded from the analyses (n = 174). As the manufacturer states that low titers of the antigen test (1.0–4.0 pg/mL for salivary specimens and 1.0–10.0 pg/mL for nasopharyngeal swab specimens) can induce false positives and recommends confirmation with RT-PCR, we defined such cases as antigen-negative for the analyses. For those with a positive antigen result, laboratory confirmation was performed using RT-PCR.[18]

This study was conducted in compliance with the Declaration of Helsinki. The institutional review board of Teine Keijinkai Medical Center approved the study (approval number 2-020260-00). Written informed consent for analyses and publication was obtained from all participants.

2.2. Data sources

Data were obtained from human resource records and electronic health records. We obtained the following data: demographics (ie, age and sex), job titles (ie, physicians, nurses, pharmacists, medical technicians, rehabilitation therapists, administrative staff, and contractors [janitors, security staff, and drivers]), and (iii) risk of contact with COVID-19 patients. According to the recommendations of the World Health Organization and the Japanese Society for Infection Prevention and Control,[19,20] the employees were grouped based on the duration of contact with COVID-19 patients as follows: high-risk contact group: individuals who had been in direct contact with non-mask-wearing COVID-19 patients without wearing any personal protective equipment (PPE) for ≥15 min; intermediate-risk contact group: those who had been in direct contact with non-mask-wearing COVID-19 patients without wearing complete PPE, such as no eye protection; and low-risk contact group: those who had been in direct contact (duration: <15 minutes) with non–mask-wearing COVID-19 patients while wearing full PPE

or those with direct contact (duration: <15 minutes) with mask-wearing COVID-19 patients while wearing at least a surgical mask. As a reference, we included a no-contact group that comprised employees who had no direct contact with COVID-19 patients. The office of infection control and prevention at our institution instructed employees who were directly involved in patient care to use PPE recommended by the World Health Organization and the Japanese Society for Infection Prevention and Control.[19,20] All data were followed-up until December 12, 2020.

2.3. Outcome

The primary outcome was a diagnosis of COVID-19, which was confirmed using the antigen test. The antigen test was positive when the titers were >4.0 pg/mL for salivary specimens and >10.0 pg/mL for nasopharyngeal swab specimens, based on the manufacturer's instructions.[16,17]

2.4. Statistical analysis

Continuous variables were expressed as means and standard deviations if they were normally distributed; otherwise, they were expressed as medians with interquartile ranges. Categorical variables were summarized as numbers and percentages. We performed a multivariable logistic regression analysis to estimate the odds ratio (OR) and 95% confidence interval (CI) to evaluate whether the contact risk and job titles were associated with COVID-19 antigen positivity. No imputation was performed for missing data, and no sensitivity analysis was performed. We used STATA version 15.1 (Stata Corp LLC, College Station, TX) and IBM SPSS Statistics version 27 (IBM, Armonk, NY) for all analyses. A 2-sided P value <.05 was considered statistically significant.

3. Results

3.1. Timeline of COVID-19 outbreak

The first COVID-19 case among the hospitalized patients was detected on November 18, 2020. Employees who worked at our institution were tested for the SARS-CoV-2 antigen on November 18, 2020. Cluster isolation in COVID-19 wards was instituted from November 21, 2020, to December 7, 2020, to prevent the spread of an outbreak. On December 12, 2020, 14 days after the last COVID-19 case among the hospitalized patients was observed, resolution of the outbreak was declared by the Sapporo City Public Health Office. During this period, a total of 44 persons, including 25 hospitalized patients and 19 hospital employees, were infected with COVID-19.

3.2. Characteristics of the study participants

A total of 1615 hospital employees were tested for SARS-CoV-2 antigen (101 physicians, 859 nurses, 51 pharmacists, 134 medical technicians, 96 rehabilitation therapists, 304 administrative staff, and 70 contractors). Among the employees, the median age was 32 years, and 21% were men. Concerning the contact risk, 91%, 7%, and 2% of the employees were classified into the no-contact, low-risk contact, and intermediate-risk contact groups, respectively. No employee was classified into the high-risk contact group (Table 1).

Table 1

Characteristics of the study participants.

Demographics	All (n = 1615)
Age, y (25%, 75%)	32 (26, 43)
Men, n (%)	334 (21)
Job titles	
Physician, n (%)	101 (6)
Nurse, n (%)	859 (53)
Pharmacist, n (%)	51 (3)
Medical technician, n (%)	134 (8)
Rehabilitation therapist, n (%)	96 (6)
Administrative staff, n (%)	304 (19)
Contractors, n (%)	70 (4)
Contact risk groups	
No-contact, n (%)	1469 (91)
Low-risk contact, n (%)	114 (7)
Intermediate-risk contact, n (%)	32 (2)
High-risk contact, n (%)	0

3.3. SARS-CoV-2 antigen positivity rate

Overall, 19 employees (1.2%) tested positive for the SARS-CoV-2 antigen (Table 2). Among the seven job titles, the positivity rate was the highest in rehabilitation therapists (2.1%), followed by nurses (1.6%), contractors (1.4%), physicians (1.0%), and administrative staff (0.3%). No positive serology was observed among pharmacists and medical technicians. Of the 4 contact risk groups, the positivity rate was the highest in the low-risk (6.1%), followed by the intermediate-risk (3.1%) and no-contact (0.7%) groups. Seventeen antigen-positive employees had a positive result in the RT-PCR confirmation test.

3.4. Predictors of SARS-CoV-2 antigen positivity

We evaluated possible predictors of SARS-CoV-2 antigen positivity, including job titles and contact risk, using logistic regression models. In the multivariable analysis, only the low-risk contact group (with the no-contact group as a reference; OR, 8.67; 95% CI, 3.30–22.8) was associated with SARS-CoV-2 antigen positivity (Table 2). There was no association between job titles and antigen positivity.

4. Discussion

This study showed that the SARS-CoV-2 antigen positivity rate was 1.2% during the hospital outbreak. Although specific jobs were not related to an increased risk of antigen positivity, employees who had a low-risk contact with COVID-19 patients presented a higher risk.

Our finding that the overall antigen positivity of COVID-19 at a Japanese tertiary medical center was 1.2% would make a significant contribution to the literature concerning the results of hospital-wide screening for COVID-19 outbreaks. Several studies[7–9] have investigated the seroprevalence of SARS-CoV-2 IgG antibodies among hospital staff; however, they did not detect current infections because antibodies usually start developing within 1 to 3 weeks after infection with SARS-CoV-2, and a positive antibody test only implies a past infection.[21] Additionally, in Japan, antibody tests are only available for research purposes.[22] In contrast, antigen testing and RT-PCR can be commercially utilized in Japan and can detect current infection with COVID-19.[12–14,22] Despite the greater sensitivity of RT-PCR compared with antigen testing, we decided to use the latter because its results are more rapidly available.[15,23] This allows for the quick identification of individuals infected with SARS-CoV-2 and the implementation of infection control strategies in outbreak settings.

Additionally, our finding that employees in the low-risk contact group had a significantly higher risk of antigen positivity compared with those in the no-contact group was consistent with the results of a prior study from England that reported that SARS-CoV-2 IgG seropositivity was only found in health care workers who had direct contact with COVID-19 patients.[9] However, the results should be interpreted with caution because there are differences in the sample populations, definitions of the risk groups, and choice of diagnostic tests. We also found that most positive antigen test results were observed in the no-contact and low-risk contact groups. The reasons for this remain unclear, but a possible explanation could be that the local hygiene standard was not effectively implemented. Employee education regarding the proper use of PPE should be continued, and institutional surveillance to evaluate adherence to hygiene standards may be needed in all departments of our institution. Another possible explanation is that SARS-CoV-2 transmission might occur in individuals without symptoms. Available evidence suggests that

Table 2

Predictors of COVID-19 antigen positivity.

	Antigen-positive, n (%) (n = 19)	Antigen-negative, n (%) (n = 1596)	Odds ratio (95% CI)	P
Contact risk groups				
No-contact	11 (0.7)	1458 (99.3)	Reference	
Low-risk	7 (6.1)	107 (93.9)	8.67 (3.30–22.8)	.001
Intermediate-risk	1 (3.1)	31 (96.9)	4.28 (0.54–34.2)	.17
High-risk	0	0	NA	NA
Job titles				
Administrative staff	1 (0.3)	303 (99.7)	Reference	
Physician	1 (1.0)	100 (99.0)	3.03 (0.19–48.9)	.44
Nurse	14 (1.6)	845 (98.4)	5.02 (0.66–38.3)	.12
Pharmacist	0 (0.0)	51 (100)	NA	NA
Medical technician	0 (0.0)	134 (100)	NA	NA
Rehabilitation therapist	2 (2.1)	94 (97.9)	6.45 (0.58–71.9)	.13
Contractor	1 (1.4)	69 (98.6)	4.39 (0.27–71.1)	.30

CI = confidence interval, NA = not applicable.

asymptomatic or presymptomatic individuals may have comparable infectivity of the virus to symptomatic COVID-19 patients.[24–27] It remains unclear whether this had occurred during the study period; nevertheless, our results suggested that conventional infection control measures are insufficient, and strategic testing of asymptomatic healthcare workers who are at risk for being exposed to COVID-19 patients is required to control hospital outbreaks of COVID-19 successfully. Additionally, several employees in the low-risk contact group may have been infected in the community. Post-hoc individual interviews revealed that two individuals in the low-risk group had contacts with COVID-19 patients at the household level, whereas those in other groups did not have such contact.

Finally, the lack of association between job titles and antigen positivity in our results is reassuring information for health care workers who are delivering care for COVID-19 patients. This is because several studies have reported that front-line health care workers experience harassment and stigma, such as verbal abuse and social devaluation, associated with COVID-19.[28–30] This is a human rights violation that should be condemned.[31] We believe that our results may contribute to eliminating such behaviors to protect the limited health care human resources.

This study had several limitations. First, our results may not be generalizable to other settings because this was a single-center study. Second, unmeasured confounding factors may have existed because of the observational study design. Third, there is a possibility of false-negative results in antigen testing.[14,15] However, we considered the pre-test probability of infection to be high because high community infection rates were recorded in Sapporo area during the outbreak.[32] Fourth, there is a possibility of false-positive results of antigen testing; however, we tried to minimize this risk by categorizing employees with low titers of antigen as having negative viral serology and confirming the diagnosis with RT-PCR assay for those who were tested as antigen-positive.[13,14,17,18] Indeed, 2 of the 19 antigen-positive employees had a negative RT-PCR result. Fifth, we did not perform whole viral genome sequencing[11] to determine the source of infection; however, we conducted this study using the maximum available research resources in our medical center. Finally, owing to the small number of employees with a positive antigen test result, our study was not adequately powered to detect all potentially significant differences.

In conclusion, this study showed that the antigen positivity rate during a nosocomial outbreak at a Japanese tertiary institution was low and suggested that assessing the risk of contact with COVID-19 patients, rather than the employees' job titles, was more important to identify hospital staff infected with COVID-19. Our findings may add to the growing evidence for clinicians, hospital managers, public health practitioners, and political leaders concerning the risks and benefits of mass screening for the COVID-19 pandemic.

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Author contributions

Research idea and study design: YS, HK, JO, YF; data acquisition: YS, HK, JO, YF; data analysis/interpretation: YS, HK, JO, YF; statistical analysis: YS, HK, JO, YF; supervision or mentorship: YF. Each author provided important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Conceptualization: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Data curation: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Formal analysis: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Investigation: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Methodology: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Project administration: Yasushi Furuta.

Resources: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Software: Yoshinosuke Shimamura.

Supervision: Yasushi Furuta.

Validation: Yoshinosuke Shimamura.

Visualization: Yoshinosuke Shimamura, Junko Oikawa.

Writing – original draft: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

Writing – review & editing: Yoshinosuke Shimamura, Hiroki Komazawa, Junko Oikawa, Yasushi Furuta.

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