Factors associated with SARS-CoV-2 symptomatic infection in university students: a school-wide web-based survey during the Omicron variant outbreak

Mai Katahira¹, Hisami Sameshima¹, Rie Tanuma¹, Kumi Setoyama¹, Yuka Yamaguchi¹, Akiyo Kamachi¹, Satoko Nakamura¹, Mayuko Sakuma¹, Yoichi Kawaike¹, Tamotsu Furuya¹, and Shinji Ijichi¹

¹Kagoshima University

August 14, 2023

Abstract

Background: The Omicron outbreak is characterized by breakthrough infection and reinfection. If no strategic solution can be found, vaccination-rate-based risk compensation may prolong the COVID-19 crisis. Infection control in university students may have an indirect impact on the COVID-19 burden for other age groups

Methods: To reveal the association between related factors and a symptomatic episode of COVID-19, a school-wide web-based questionnaire survey was conducted among university students as a part of the annual health check-up in April, 2023. The positive outcome was confined to the first symptomatic onset during the Omicron variant outbreak.

Results: In this self-administered and non-observational survey, risk or protective associations were merely estimated statistically in university students (n = 5,406). In measured factors, karaoke and club/group activities could maintain the statistical significance in adjusted odds ratios (ORs) as (relative) risk factors, and science course, measles/rubella (MR) vaccination, and COVID-19 vaccination remained as (relative) protective factors in adjusted OR analyses. Club/group activities (with member gathering) and karaoke sing-along sessions in university students may frequently have WHO’s three Cs. These risk factors are still important topics for the infection control of COVID-19 in university students. Together with some recent reports from other researchers, the significant protective role of MR vaccine in our survey warrants further clinical investigation.

Conclusions: If the breakthrough infection continuously constitutes the majority of infection, real data in test-negative case-control or web-based questionnaire design continue to be important for statistical analysis to determine the minimal requirement of our strategies which may replace COVID-19 vaccines.
Abstract

Background: The Omicron outbreak is characterized by breakthrough infection and reinfection. If no strategic solution can be found, vaccination-rate-based risk compensation may prolong the COVID-19 crisis. Infection control in university students may have an indirect impact on the COVID-19 burden for other age groups.

Methods: To reveal the association between related factors and a symptomatic episode of COVID-19, a school-wide web-based questionnaire survey was conducted among university students as a part of the annual health check-up in April, 2023. The positive outcome was confined to the first symptomatic onset during the Omicron variant outbreak.

Results: In this self-administered and non-observational survey, risk or protective associations were merely estimated statistically in university students (n = 5,406). In measured factors, karaoke and club/group activities could maintain the statistical significance in adjusted odds ratios (ORs) as (relative) risk factors, and science course, measles/rubella (MR) vaccination, and COVID-19 vaccination remained as (relative) protective factors in adjusted OR analyses. Club/group activities (with member gathering) and karaoke sing-along sessions in university students may frequently have WHO’s three Cs. These risk factors are still important topics for the infection control of COVID-19 in university students. Together with some recent reports from other researchers, the significant protective role of MR vaccine in our survey warrants further clinical investigation.

Conclusions: If the breakthrough infection continuously constitutes the majority of infection, real data in test-negative case-control or web-based questionnaire design continue to be important for statistical analysis to determine the minimal requirement of our strategies which may replace COVID-19 vaccines.

KEYWORDS: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), Omicron variant, risk behaviors, protective factors, measles/rubella (MR) vaccine, confounders

INTRODUCTION

The surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants is repeatedly updating the pandemic peak of the coronavirus disease 2019 (COVID-19) even after the roll-out of vaccines. Omicron variant has emerged with increased transmissibility at a time when vaccine immunity is increasing in the world. The transmissibility is associated or may share the part of mechanism with increased viral shedding, higher viral binding affinity, higher immune escape, biased tissue tropism, and lesser impact on host fitness. Because the Omicron outbreak is characterized by breakthrough infection and reinfection, the molecular mechanisms including antibody-dependent enhancement of infection may actually be active in the transmission processes for the virus to survive. In this evolutionarily carved landscape, efforts to find the strategic solution should be continued. Without such efforts, vaccination-rate-based risk compensation may promote the virus survival. Infection control in university students may have an indirect impact on the COVID-19 burden for other age groups, and better understanding of the clinical features of COVID-19 risk in young populations has current and future policy implication not only for COVID-19 but also for the next infectious respiratory disease by a novel virus.

Questionnaire survey is still one of the data collection tools to investigate complex factors affecting human behaviors and clinical outcomes. Self-administered questionnaire survey can provide generalizable adjusted odds ratios (ORs) of exposure-outcome associations even when the response rate is considerably low (18%). Both the critical exposure (including vaccination) as the result of non-randomized allocation...
and the diagnostic outcome during the period of interest can be evaluated in a regional-community-based survey. In addition, web-based manner using a variety of internet platforms can optimize and accelerate the data collection and processing with the spread of personal internet access devices (smartphone). Large-scale survey can increase the statistical implications. Here, related variables for COVID-19 symptomatic onset during Omicron variant outbreak are assessed using a web-based questionnaire survey among students in a Japanese university, Kagoshima University.

METHODS

Study design and sample constitution

A school-wide web-based questionnaire survey was launched in conjunction with the annual health checkup (web version) in April, 2023. Authenticated eligible students in Kagoshima University could access the questionnaire and their answers could be revised repeatedly by themselves for more than two months (until Jun. 15th, 2023). In this self-administered and non-observational survey, risk or protective associations were merely estimated statistically.

Instructions for the annual health checkup were informed to every student in Kagoshima University using documents, e-mails, home page contents, bulletin boards, and banner-flags. In order to make the outcome variable to be symptomatic infection with Omicron variants, cases with the first onset prior to the beginning of Omicron surge (Jan 2022) are not included in the participants. A symptomatic episode and positive result of COVID-19 testing [antigen test or polymerase chain reaction (PCR)] are prerequisites for the inclusion as infected students.

2.2 Variable definitions (Table 1)

Vaccination campaign was rolled out in Jun. 2021 in our university using the mRNA vaccine (Moderna) without student financial burden. The second dose was scheduled 4 weeks after the first dose and the third vaccine dose (first booster) was provided from Mar. to Jun. in 2022. Although most vaccinated students enjoyed this campus vaccination campaign, some got vaccinated outside our university and with mixed vaccine types or brands for each dose. As an additional booster offer, mRNA bivalent vaccine (Moderna) was provided from Oct. 13, 2022 in Japan. Because the positive outcome is clinical diagnosis of symptomatic COVID-19 with the first episode after the biggening of 2022 as described above, in infected individuals, most of the vaccinated students have completed the last dose more than 2 months prior to the outcome. Related variables were obtained from two questionnaire sections, the annual health checkup section and the newly added questions. Each section has two types of questions, history taking (retrospective manner) and questions to detect present or recent conditions (cross-sectional manner). The outcome variable and vaccine doses were binarized using answers to the history taking questions as shown in Table 1. Because Japanese students have usually gotten vaccinated with measles/rubella (MR) vaccine doses in childhood, the MR vaccine variable is a marker of parental vaccine policy. BMI was calculated as weight/height$^2$(kg/m$^2$) using self-declared data and categorized as low (<18.5 kg/m$^2$), normal (18.5-24.9 kg/m$^2$), and high (>25 kg/m$^2$). The BMI variables, BMI low and high, were binarized as shown in Table 1. The annual health checkup section includes 4 questions to select students who have health concerns including past history abnormalities and positive family histories of heart diseases. Students who registered a “Yes” response to one or more of these questions are automatically instructed to make a web-based reservation for face-to-face checkup with a medical doctor. Such students with health concerns were 14.1% of the final participants. Questions to estimate club/group, travel, and karaoke activities of university students were simplified for smart phone response and prepared to avoid too few “Yes” responses as shown in Table 1.

2.3 Statistical analyses

Generalized linear model (GLM) was implemented for multivariate logistic regression with the outcome variable of symptomatic Omicron infection using R software version 4.3.0 (The R Foundation). Every combination between the outcome and predictor variables was preliminarily tested by chi-square analysis using R to predict the presence of associations. Confounding effects were controlled among the outcome-
associated variables using adjusted OR by combination with one of the COVID-19 vaccine dose variables, [?]1 dose, [?]2 doses, or [?]3 doses. To show confounder-rich association between the predictor variable and outcome, GLM outputs without statistical significance were shown as missing of adjusted OR data. Effect modification by inter-variable interactions were evaluated by the involvement of every combination of the predictor candidates. A $p$-value $< 0.05$ was considered to be statistically significant, and a 95% confidence interval (CI) was presented with ORs.

2.4 Ethical consideration

Ethical clearance was obtained from the institutional ethical review board, Ethics Committee of the Health Service Center, Kagoshima University (accession no.: R4-5-1). A question for participation consent was included in the questionnaire in the health checkup, and students with disagreement were excluded from this study.

RESULTS

The university has an enrollment of 10,144 students in academic year 2023 (Figure 1). Non-responders were 3,350 students with a response rate of 67.0%. 990 students refused to allow their answers to be anonymously utilized for community or society with a consent rate of 85.4%. 218 infected students in the consented students answered that the clinical diagnosis had been made without COVID-19 testing (antigen test or PCR) and were excluded from the subjects. 99 COVID-19 cases with asymptomatic first episode and 81 infected cases with the first onset prior to the beginning of Omicron surge were also excluded from the participants. Then, the infected students (31.5%) were characterized as COVID-19 test-proven symptomatic infection of Omicron variants. Because the final sample (n = 5,406) included 2 individuals without data of self-declared weight and height, only body mass index (BMI)-associated analyses were implemented in 5,404 students (Figure 1). Male/female ratio was 1.55 in the 2023 enrollment, and 1.11 in the final participants as shown in Figure 1. 87.7% (n = 1,485) of infected students (n = 1,693) were fully vaccinated with COVID-19 vaccines ([?]2 doses), and 92.2% (n = 3,413) of uninfected students (n = 3,703) were fully vaccinated.

3.1 Risk and protective associations

Associations between the outcome variable (symptomatic infection with Omicron variants) and each predictor candidate were assessed using chi-square test ($p < 0.05$) (Table 2). Relative risk associations were revealed in present smoking, high karaoke activities, male gender, high club/group activities, and high travel activities. Relative protective associations were demonstrated in science course, measles/rubella vaccination ([?]2 doses), and COVID-19 vaccination (each dose). Other predictor candidates including present persistent cough, the first academic year, the presence of health concerns, BMI extremes (high or low), and internationality, had no significant association with the outcome variants (Figure 2). Crude ORs with 95% CI were distributed in accordance with the results of chi-square test (Figure 2). The 95% CIs of the ORs of candidates without significant association contained the OR value 1.

3.2 Adjusted ORs

Predictor variables with significant association with symptomatic Omicron infection were involved in the GLM regression calculation. In some variables, the statistical significance was disappeared from the GLM outputs (Table 2), suggesting the presence of confounding networks with other listed variables. Adjusted ORs for present smoking, male gender, and travel activities could not maintain the significance (Table 2). Adjusted OR for measles/rubella vaccination maintained the statistical significance in the GLM outputs as a protective factor of symptomatic Omicron infection.

3.3 Variable interactions

Every pair of predictor candidates including factors without association with symptomatic Omicron infection was involved in the GLM regression calculation with interactions (the last column of Table 2). Statistically significant variable interactions (effect modifications) were demonstrated in pairs with low BMI and a pair of a risk variable (smoking) and a factor without association (health concerns); science course$\times$low BMI
genic homology between viruses, and MR vaccinations (Table 3), there was no significant interaction (effect modifications) between these two protective factors in the interaction GLM outputs (Table 2). In students boosted with COVID-19 vaccines, the risk situations (present smoking, karaoke activities, and male gender) were significantly fewer. The risk situations (present smoking and male gender) were also significantly fewer in students fully vaccinated with MR vaccine. A risk situation (high club/group activities) was more frequently found in MR fully vaccinated students with a statistical significance (Table 3).

DISCUSSION

In this self-administered and non-observational survey, risk or protective associations were merely estimated statistically in university students (n = 5,406). Risk associations with symptomatic infection with Omicron variants were statistically (chi-square test) detected in present smoking, high karaoke activities, male gender, high club/group activities, and high travel activities. Protective associations were demonstrated in science course, measles/rubella vaccination ([?]2 doses), and COVID-19 vaccination. The statistical significance of present smoking, male gender, and travel activities were disappeared in GLM outputs to calculate adjusted ORs (Table 2), suggesting the presence of confounding networks with other listed variables. In measured factors, karaoke and club/group activities could maintain the statistical significance as risk factors, and science course, MR vaccination, and COVID-19 vaccination remained as protective factors in GLM outputs (Table 2). Social gathering and karaoke sessions provide high risk environments for SARS-CoV-2 infection in Japan, and club/group activities (with member gathering) and karaoke sing-along sessions in university students may frequently have WHO’s three Cs (crowded places, close-contact settings, and confined and enclosed spaces). These risk factors are still important topics in cautions for university students to control the transmission. GLM outputs with variable interactions (effect modifications) and chi-square analyses between variables suggested the presence of more complex connections of predictive variables. In this GLM implement, adjusted ORs for smoking and male gender maintained the statistical significance (Table 2). A risk factor (karaoke activities) and a protective factor (MR vaccination) were much affected by measured confounders including interactions. The statistically significant and reconfirmed (using GLM) interactions were science course×low BMI (risk direction) and male gender×low BMI (protective direction) (Table 2). Critical clinical clues or keys to terminate COVID-19 prevalence may hidden in this complex relationship of predictive factors including unmeasured confounders and interactions.

Because MR vaccination is usually included in childhood vaccination campaign in Japan, the MR vaccination uptake depends on domestic surroundings under strong influence of parental decision-making. At present, vaccinated students have usually gotten fully vaccinated with MR vaccines at least 10 years prior to admission. Same as our results shown in Figure 2 and Table 2, MR vaccine had been characterized in previous reports as one of the protective factors of COVID-19. Possible preventive or mitigating effects of measles, mumps, and rubella (MMR) vaccine could be explained by an induction of innate immunity, anti-agnostic homology between viruses, and specific or non-specific enhancement of COVID-19 vaccine response. The B cell cross-reactivity with SARS-CoV-2 antigens was also reported in MR-vaccinated children and adults, and statistical correlation between the SARS-CoV-2-specific B cell activation and serum level of anti-measles antibody was suggested. On the other hand, there are some negative data on the protective role of such live attenuated vaccines against COVID-19 outcomes. Our results warrant further investigation on unmeasured confounders or interactions (effect modifications) around the possible protective factor (MR vaccination). Although the independence was statistically denied using chi-square test between COVID-19 and MR vaccinations (Table 3), there was no significant interaction (effect modifications) between these...
two protective factors in the interaction GLM outputs (Table 2), suggesting the modification of COVID-19 vaccine response by MR vaccine may be not plausible.

No vaccine may be 100% effective. Therefore, growing vaccine coverage in the population and prolonged infection prevalence causes an increase of vaccinated cases in infected individuals (87.7% in our survey). The breakthrough infection is one of the characteristics of Omicron variants of SARS-CoV-2 and the apparent persistence of breakthrough infection may warrants reconsideration of vaccine strategies. However, if this situation remained unchanged, we should continue to investigate the complexity behind and beyond the risk and protective factors of the infection. Mechanisms which increase the ratio of vaccinated cases in infected individuals include a possible link between inoculation behavior and the accessibility to COVID-19 tests at symptomatic onset, and an association between vaccination and frequent social interactions or potentially hazardous behaviors. As possible backgrounds which decrease the ratio of unvaccinated people in the documented infection, the link between inoculation behavior and risk reduction behavior and the biased presence of undocumented infection with COVID-19 in unvaccinated individuals were speculated. If unvaccinated patients were more registered as vaccination-unknown inputs in interview designs, the vaccinated counterpart in infected patients may be underestimated. The presence of undocumented infection with SARS-CoV-2 in unvaccinated individuals and the low accessibility to PCR or antigen test in unvaccinated infection were previously suggested by small scale studies. These mechanisms were not supported by our survey. The inoculation behaviors (MR and COVID-19 vaccination) had a protective association with COVID-19 symptomatic diagnosis (Figure 2 and Table 2), and the more COVID-19 vaccination doses, the fewer social activities and risk behaviors they have (Table 3). Although there is almost no ‘unknown’ input on COVID-19 vaccination status in our university student questionnaire, the vaccination rate of infected individuals was quite high (87.8%). Concerning documentation of infection in our university, students who wish apply for academic relief or helps for COVID-19-associated absences from university class must register their symptomatic onset to a web-registration system with the information of the COVID-19-test result. Therefore, the accessibility to PCR or antigen test may be quite high in both vaccinated and unvaccinated students without apparent difference between them in our university.

LIMITATIONS

Non-observational school-wide survey using a web-based questionnaire has some limitations. Answers to the questionnaire can be affected by student’s memory biases and subjective instability. For the responders to ascertain and retrieve their answers, the access to the questionnaire were unlimited for more than two months as described in method. The response to the questionnaire was imposed on students as a part of the annual health check-up (web version) and the response rate was 67.0%. Selection biases may be involved in withdrawal of male students (Figure 1) and invisible or arbitrary (n = 99) exclusion of asymptomatic episodes. Because male gender was one of the risk candidates with confounders, the male withdrawal may cause obscuration of the risk associations. Although university students are relatively homogenous regarding age, life circumstances, and field range of activities, there may be a lot of unmeasured or unknown confounders. Involvement of multiple risk or protective candidates in multivariate logistic regression analysis may be critical for reliable implementation of large-scale web-based questionnaire survey. Even in view of these limitations, our report has an important priming significance that warrants further investigations including observational prospective studies.

CONCLUSION

Risk circumstances for SARS-CoV-2 infection in university students were club/group activities (with member gathering) and karaoke sing-along sessions, which were previously suggested in a report using test-negative case-control design. MR vaccine had been characterized as a protective factor of COVID-19 and the protective significance in symptomatic Omicron infection was reconfirmed in our study. These reproducibility of risk or protective significance in related factors supports the reliability and implication of our web-based questionnaire survey. If the virus variants continue to be characterized by breakthrough infection and reinfection, the effort to accumulate clinical real data in test-negative case-control or web-based questionnaire design must be continued for statistical analysis to determine the minimal requirement of our strategies.
which may replace COVID-19 vaccines.

**AUTHOR CONTRIBUTIONS**


**DATA AVAILABILITY STATEMENT**

Data in R-style will be made available on request.

**REFERENCES**


Figure titles and legends

Figure 1. Flowchart outlining data exclusion to evaluate associations between a symptomatic episode of COVID-19 and related factors during the Omicron variant outbreak. The questionnaire survey was executed in conjunction with 2023 annual health checkup for Kagoshima university students.

Figure 2. Crude odds ratios (OR) and 95% confidence intervals for association between predictor candidates and the outcome variable (symptomatic infection with Omicron variants). Red round markers indicate data of risk or protective associations with statistical significance (chi-square test, \( p \)-value < 0.05).

Hosted file