Scientific Research Publishing

Advances in Infectious Diseases, 2024, 14, 133-146
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Symptomatic COVID-19 in University Students: A School-Wide Web-Based Questionnaire Survey during the Omicron Variant Outbreak

Mai Kitahara[1], Hisami Sameshima[1], Rie Tanuma[1], Kumi Setoyama[1], Yuka Yamaguchi[1], Akiyo Kamachi[1], Satoko Nakamura[1], Mayuko Sakuma[1], Yoichi Kawaike[1], Tamotsu Furuya[2], Shinji Ijichi[1*]

[1]Health Service Center, Kagoshima University, Kagoshima, Japan
[2]Center for Management of Information Technologies, Kagoshima University, Kagoshima, Japan
Email: *jiminy@hsc.kagoshima-u.ac.jp

How to cite this paper: Kitahara, M., Sameshima H.,, Tanuma, R., Setoyama, K., Yamaguchi, Y., Kamachi, A., Nakamura, S., Sakuma, M., Kawaike, Y., Furuya, T. and Ijichi, S. (2024) Symptomatic COVID-19 in University Students: A School-Wide Web-Based Questionnaire Survey during the Omicron Variant Outbreak. *Advances in Infectious Diseases*, **14**, 133-146.
https://doi.org/10.4236/aid.2024.141010

Received: December 27, 2023
Accepted: January 30, 2024
Published: February 2, 2024

Abstract

Aim: To detect risk and preventive factors associated with the Omicron variant infection in university students, a combination of a web-based survey and multivariate logistic regression analysis was introduced as the front-line initiatives by the school health practitioners. **Design:** Questionnaire survey. **Methods:** The school-wide web-based questionnaire survey was conducted among our university students as a part of the annual health check-up in April, 2023. The positive outcome was confined to the first symptomatic COVID-19 onset during the Omicron variant outbreak. **Results:** In this self-administered survey, risk or protective associations were merely estimated statistically in university students (n = 5406). 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. 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 be equivalent to or 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

1. 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 [1]. Because the Omicron outbreak is characterized by breakthrough infection and reinfection [2], the molecular mechanisms including antibody-dependent enhancement of infection [3] may actually be active in the transmission processes for the virus to survive. In this evolutionarily carved landscape, efforts to find the effective solution for infection control should be continued. Without such efforts, vaccination-rate-based risk compensation [4] may promote the virus survival.

Infection control of COVID-19 in schools and campuses is a global policy priority, but detecting risk behaviors in children and adolescents is still challenging [5]. Subtle interactions between infection-protective behaviors and risks may be involved in the increase of COVID-19 in vaccinated individuals [6] [7]. The impact of the COVID-19 pandemic on children/youth further highlighted the important role of school health practitioners in infection control initiatives in schools and campuses [8] [9], and they are viewed as a credible, tailored, and sometimes only source of COVID-19 information [10] [11]. Infection control in university students may have an indirect impact on the COVID-19 burden for other age groups [12], 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. As a practical effort with a low burden on school staff both in terms of time and budget, a web-based questionnaire survey in combination with statistical analyses using R (free statistical software) was implemented for Omicron variant prevention strategies.

2. Methods

2.1. 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. As a result, the response rate can be increased more than independent implementation and fundamental variables can be available from the annual health checkup questions (**Table 1**). 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

Table 1. Definitions of variables.

	Binary 1	Reference (0)
Gender	Male (52.7%)	Female
Academic year (first)	First (28.9%)	≥Second
Course	Science (68.7%)	Humanities
Outcome variable: "How many times did you get infected with COVID-19?"	≥1 (31.5%)	Un-infected
COVID-19 vaccine: "How many times did you get vaccinated for COVID-19?"	≥1 dose (92.2%)	Un-vaccinated
	≥2 doses (90.8%)	<2 doses
	≥3 doses (66.9%)	<3 doses
Measles/rubella (MR) vaccine: "Have you got vaccinated for MR more than or equal to twice?"	Yes (72.0%)	No
Smoking: "Do you smoke?"	Yes (2.8%)	No
Persistent cough: "Do you have a persistent cough for more than two weeks?"	Yes (0.5%)	No
BMI low	BMI < 18.5 (14.2%)	BMI ≥ 18.5
BMI high	BMI ≥ 25.0 (10.0%)	BMI < 25.0
Health concerns including past history abnormalities (4 questions)	Yes (14.1%)	No (every 4 question)
Club or group activities: "Are you recently joining in club or group activities?"	Yes (40.7%)	No
Travel activities: "Is your travel activity recently high (≥twice per year)?"	Yes (58.2%)	No
Karaoke activities: "Is your karaoke activity (group) recently high (≥once per month)?"	Yes (19.8%)	No
International students: "Are you a student from abroad?"	Yes (2.4%)	No

To increase response rate of the questionnaire survey, questions are simplified and carefully selected for smart phone access. Only essential questions for the variables are presented. Gender, academic year, and course are obtained from student personal information in connection with I.D., and body mass index (BMI) was calculated with self-declared weight and height.

questionnaire survey, following the exclusion criteria being applied to the 5,804 responders with informed consent (Figure 1), 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) [13] 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. The exclusion processes to evaluate associations between a symptomatic episode of COVID-19 and related factors during the Omicron variant outbreak are depicted in Figure 1.

2.2. Questions and Variable Definitions (Table 1)

Vaccination campaign was rolled out in Jun. 2021 in our university using the

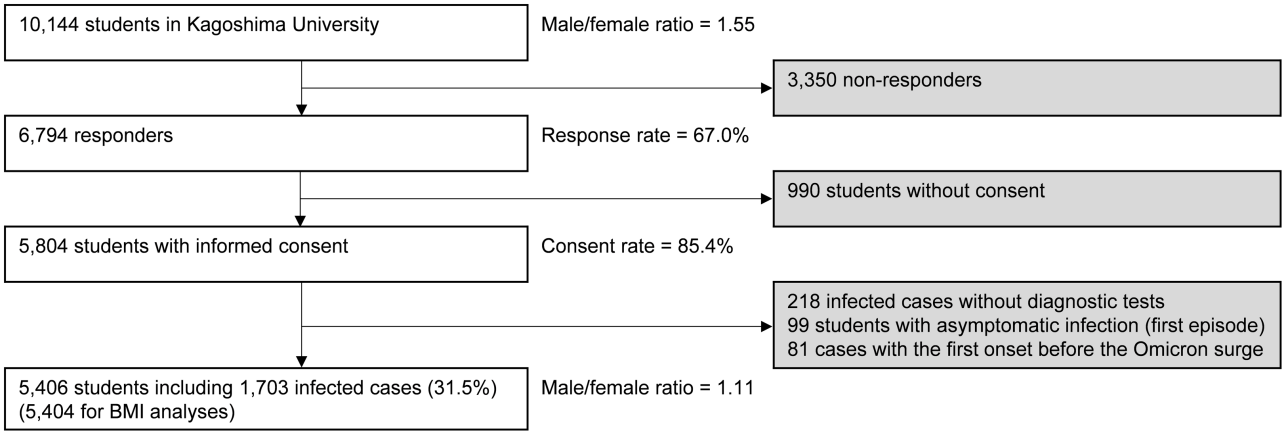

Figure 1. Flowchart outlining data exclusion to evaluate associations between a symptomatic episode of COVID-19 and related factors during the Omicron variant outbreak. The questionnaire survey was executed in conjunction with 2023 annual health checkup for Kagoshima university students.

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 type and questions to detect present or recent conditions (Table 1). 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. Newly added 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. Questions for COVID-19 vaccination and internationality

were also newly added. These questions were all added to evaluate the risk or preventive factors for COVID-19, and the real associations were objectively confirmed by statistical analyses. Because too many questions or a too long query may cause answer interruption, the number and texts of newly added questions were considered repeatedly. In order to evaluate the presence of confounding factors and interactions between predictors, associations with symptomatic COVID-19 were statistically evaluated in as many variables as possible.

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). This analysis can make it possible to evaluate the presence of confounding factors and the interactions between predictors (effect modifications) [14]. 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 odds ratio (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. Ethics Approval

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.

3. Results

The university has an enrollment of 10,144 students in academic year 2023 (**Figure 1**). Non-responders were 3350 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 sam-

ple (n = 5406) included 2 individuals without data of self-declared weight and height, only body mass index (BMI)-associated analyses were implemented in 5404 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. 87.8% (n = 1495) of infected students (n = 1703) were fully vaccinated with COVID-19 vaccines (≥2 doses), and 92.2% (n = 3413) of uninfected students (n = 3703) 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) and ORs (Figure 2). Relative risk associations were revealed in present smoking, high karaoke activities, male gender, 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

Table 2. Crude and a djusted odds ratios (ORs) for factors associated with COVID 19 symptomatic infection in university students.

Factors		COVID-19		*p*-value (chi-square test)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI) with interactions
		Infected	Uninfected				
Smoking	Yes	60	89	0.02	1.48 (1.06 - 2.07)		1.45 (1.01 - 2.08)
	No	1643	3614				
Karaoke activities	High	402	671	$<1 \times 10^{-5}$	1.40 (1.21 - 1.61)	1.33 (1.15 - 1.53)	
	Low	1301	3032				
Gender	Male	943	1906	0.01	1.17 (1.04 - 1.13)		1.21 (1.06 - 1.38)
	Female	760	1797				
Club or group activities	Yes	737	1462	0.01	1.17 (1.04 - 1.13)	1.17 (1.04 - 1.32)	1.19 (1.05 - 1.34)
	No	966	2241				
Travel activities	High	1027	2120	0.03	1.13 (1.01 - 1.28)		
	Low	676	1583				
Course	Science	1115	2601	<0.001	0.80 (0.71 - 0.91)	0.81 (0.72 - 0.92)	0.73 (0.63 - 0.83)
	Humanities	588	1102				
Measles/rubella vaccine	≥2 doses	1172	2720	<0.001	0.80 (0.70 - 0.91)	0.84 (0.74 - 0.96)	
	≤1 dose	531	983				
COVID-19 vaccine	≥3 doses	1002	2616	$<1 \times 10^{-15}$	0.59 (0.53 - 0.67)	0.61 (0.54 - 0.68)	0.60 (0.53 - 0.68)
	≤2 doses	701	1087				

Adjusted OR with 95% confidence intervals (CI) was computed using generalized linear model (GLM) for factors with significant *p*-values (chi-square test, <0.05). Missing data in adjusted ORs indicate the GLM outputs cannot reach statistical significance. The last column is a GLM analysis with interactions, and every pair of predictor candidates was initially involved. Statistically significant combinations were course × BMI (low), gender × BMI (low), and smoking × health concerns, in this output.

low), and internationality, had no significant association with the outcome variables (Figure 2).

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 × low BMI (adjusted OR = 1.61 with CI: 1.12 - 2.31), male gender × low BMI (adjusted OR = 0.64 with CI: 0.45 - 0.90), and present smoking × health concerns (adjusted OR = 0.28 with CI: 0.09 - 0.90). The significance

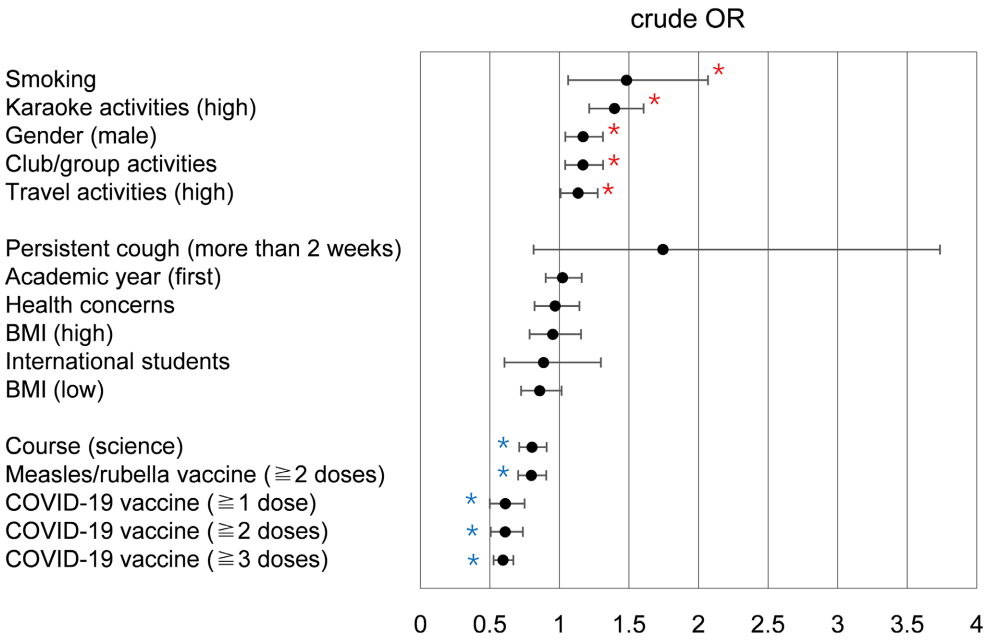

Figure 2. Crude odds ratios (OR) and 95% confidence intervals for association between predictor candidates and the outcome variable (symptomatic infection with Omicron variants). Statistically significant (chi-square test, p-value < 0.05) relative risk associations were shown with red asterisks and relative protective associations with statistical significance (chi-square test, p-value < 0.05) were presented with blue asterisks.

in low BMI-associated interactions were reconfirmed in R outputs whose family is binomial with link = log (data not shown) [14]. To confirm the statistically significant interactions, GLM outputs were repeated in subgroups of the participants. In low BMI students (n = 766), adjusted OR of science course was increased and the protective significance was disappeared and the risk significance of male gender was also masked. In students with health concerns (n = 760), the risk significance of present smoking became unclear. 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). 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 (club/group activities) was more frequently found in MR fully vaccinated students with a statistical significance (Table 3).

4. Discussion

Questionnaire survey is still one of the data collection tools to investigate complex factors affecting human behaviors and clinical outcomes [15], and self-administered questionnaire survey can provide generalizable adjusted ORs of exposure-outcome associations even when the response rate is considerably

Table 3. Chi-square analyses between variables.

Factors		COVID-19 vaccine		*p*-value (chi-square test)	Measles/rubella vaccine		*p*-value (chi-square test)
		≥3 doses	≤2 doses		≥2 doses	≤1 dose	
Smoking	Yes	64 (1.8%)	85 (4.8%)	$<1 \times 10^{-9}$	90 (2.3%)	59 (3.9%)	<0.01
	No	3554	1703		3802	1455	
Karaoke activities	High	672 (18.6%)	401 (22.4%)	<0.001	748	325	0.07
	Low	2946	1387		3144	1189	
Gender	Male	1721 (47.6%)	1128 (63.1%)	$<1 \times 10^{-15}$	1921 (49.4%)	928 (61.3%)	$<1 \times 10^{-14}$
	Female	1897	660		1971	586	
Club or group activities	Yes	1498 (41.4%)	701 (39.2%)	0.13	1632 (41.9%)	567 (37.5%)	<0.01
	No	2120	1087		2260	947	
Travel activities	High	2114	1033	0.67	2271	876	0.77
	Low	1504	755		1621	638	
Course	Science	2511	1205	0.14	2667	1049	0.61
	Humanities	1107	583		1225	465	
Measles/rubella vaccine	≥2 doses	2736 (75.6%)	1156 (64.7%)	$<1 \times 10^{-15}$			
	≤1 dose	882	632				

Values given in parentheses are percentages in students with the same vaccination uptake.

low (18%) [16]. 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 [17]. 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), and large-scale survey can increase the statistical implications.

In this self-administered survey, risk or protective associations were merely estimated statistically in university students (n = 5406) with an acceptable response rate (67.0%) [18]. Risk associations with symptomatic infection with Omicron variants were statistically (chi-square test) detected in present smoking, high karaoke activities, male gender, 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 [19], and club/group activities (with member gathering) and karaoke sing-along sessions in university students may frequently have WHO's three Cs (crowed 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 analysis, 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 be hidden in this complex relationship of predictive factors including unmeasured confounders and interactions. Further analyses with more other predictors may be warranted from these results.

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 [20] [21] [22] [23] [24]. Possible preventive or mitigating effects of measles, mumps, and rubella (MMR) vaccine could be explained by an induction of innate immunity [20], antigenic homology between viruses [21], and spe-

cific or non-specific enhancement of COVID-19 vaccine response [23]. The B cell cross-reactivity with SARS-CoV-2 antigens was also reported in MR-vaccinated children [24], and statistical correlation between the SARS-CoV-2-specific B cell activation and serum level of anti-measles antibody was suggested [22]. On the other hand, there are some negative data on the protective role of such live attenuated vaccines against COVID-19 outcomes [25] [26]. 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 (87.8% 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 warrant 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 [6], and an association between vaccination and frequent social interactions or potentially hazardous behaviors [7]. 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 [6] [7]. If unvaccinated patients were more registered as vaccination-unknown inputs in interview designs, the unvaccinated counterpart in infected patients may be underestimated [6]. 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 [6]. 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 vac-

cinated and unvaccinated students without apparent difference between them in our university.

5. Limitations

Although statistical analyses using large-scale response samples more than 5000 can make it possible to evaluate even the presence of confounding factors and the interactions between predictors, the 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 was 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%. Response rates in the range 60% - 69% can be evaluated as acceptable [18]. 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 prospective studies.

6. 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 [19]. MR vaccine had been characterized as a protective factor of COVID-19 [24] and the protective significance in symptomatic Omicron infection was reconfirmed in our study. The 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 [2], the effort to accumulate clinical real data in test-negative case-control or web-based questionnaire design must be continued by school health practitioners. Such efforts may allow statistical analyses to determine the minimal requirement of our strategies which may be equivalent to or replace COVID-19 vaccines.

Contribution of the Authors

All the authors participated in the preparation and implementation of the investigation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wolf, J.M., Wolf, L.M., Bello, G.L., Maccari, J.G. and Nasi, L.A. (2023) Molecular evolution of SARS-CoV-2 from December 2019 to August 2022. *Journal of Medical Virology*, **95**, e28366. https://doi.org/10.1002/jmv.28366

[2] Reynolds, C.J., Pade, C., Gibbons, J.M., Otter, A.D., Lin, K.-M., Muñoz Sandoval, D. *et al.* (2022) Immune Boosting by B.1.1.529 (Omicron) Depends on Previous SARS-CoV-2 Exposure. *Science*, **377**, eabq1841. https://doi.org/10.1126/science.abq1841

[3] Shimizu, J., Sasaki, T., Koketsu, R., Morita, R., Yoshimura, Y., Murakami, A. *et al.* (2022) Reevaluation of Antibody-Dependent Enhancement of Infection in Anti-SARS-CoV-2 Therapeutic Antibodies and mRNA-Vaccine Antisera Using FcR- and ACE2-Positive Cells. *Scientific Reports*, **12**, Article No. 15612. https://doi.org/10.1038/s41598-022-19993-w

[4] Buckell, J., Jones, J., Matthews, P.C., Diamond, S.I., Rourke, E., Studley, R., *et al.* (2023) COVID-19 Vaccination, Risk-Compensatory Behaviours, and Contacts in the UK. *Scientific Reports*, **13**, Article No. 8441. https://doi.org/10.1038/s41598-023-34244-2

[5] Li, F., Liang, W., Rhodes, R.E., Duan, Y., Wang, X., Shang, B., *et al.* (2022) A Systematic Review and Meta-Analysis on the Preventive Behaviors in Response to the COVID-19 Pandemic among Children and Adolescents. *BMC Public Health*, **22**, Article No. 1201. https://doi.org/10.1186/s12889-022-13585-z

[6] GOV JP (2022) The Epidemiological Significance of Documented COVID-19 Infection with Vaccination History Using the Record Systems (HER-SYS and VRS) (Ministry of Health, Labour and Welfare). https://www.mhlw.go.jp/content/10900000/000964392.pdf

[7] GOV UK (2022) COVID-19 Vaccine Monthly Surveillance Reports (Weeks 39 to 48, 2021 to 2022). https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports

[8] Cook, G., Appleton, J.V., Bekaert, S., Harrold, T., Taylor, J. and Sammut, D. (2023) School Nursing: New Ways of Working with Children and Young People during the Covid-19 Pandemic: A Scoping Review. *Journal of Advanced Nursing*, **79**, 471-501. https://doi.org/10.1111/jan.15504

[9] Pampati, S., Rasberry, C.N., Timpe, Z., McConnell, L., Moore, S., Spencer, P., *et al.* (2023) Disparities in Implementing COVID-19 Prevention Strategies in Public Schools, United States, 2021-22 School Year. *Emerging Infectious Diseases*, **29**, 937-944. https://doi.org/10.3201/eid2905.221533

[10] Dardas, L.A., Khalaf, I., Nabolsi, M., Nassar, O. and Halasa, S. (2020) Developing an Understanding of Adolescents' Knowledge, Attitudes, and Practices toward COVID-19. *The Journal of School Nursing*, **36**, 430-441. https://doi.org/10.1177/1059840520957069

[11] Rose, I.D., Murray, C., Hodges, A.M., Dyer, H. and Wallace, S. (2023) Perceived Role of the School Nurse in Providing Pertinent COVID-19 Information to the School Community: Experiences of Public Health Graduate Students With School-

Aged Children. *The Journal of School Nursing*. https://doi.org/10.1177/10598405231193429

[12] Ioannidis, J.P.A. (2021) COVID-19 Vaccination in Children and University Students. *European Journal of Clinical Investigation*, **51**, e13678. https://doi.org/10.1111/eci.13678

[13] Sarkar, A., Omar, S., Alshareef, A., Fanous, K., Sarker, S., Alroobi, H. *et al.* (2023) The Relative Prevalence of the Omicron Variant within SARS-CoV-2 Infected Cohorts in Different Countries: A Systematic Review. *Human Vaccines & Immunotherapeutics*, **19**, Article 2212568. https://doi.org/10.1080/21645515.2023.2212568

[14] Campbell, U.B., Gatto, N.M. and Schwartz, S. (2005) Distributional Interaction: Interpretational Problems When Using Incidence Odds Ratios to Assess Interaction. *Epidemiologic Perspectives & Innovations*, **2**, Article No. 1. https://doi.org/10.1186/1742-5573-2-1

[15] Ahmed, M.N.Q., Lalin, S.A.A. and Ahmad, S. (2023) Factors Affecting Knowledge, Attitude, and Practice of COVID-19: A Study among Undergraduate University Students in Bangladesh. *Human Vaccines & Immunotherapeutics*, **19**, Article 2172923. https://doi.org/10.1080/21645515.2023.2172923

[16] Mealing, N.M., Banks, E., Jorm, L.R., Steel, D.G., Clements, M.S. and Rogers, K.D. (2010) Investigation of Relative Risk Estimates from Studies of the Same Population with Contrasting Response Rates and Designs. *BMC Medical Research Methodology*, **10**, Article No. 26. https://doi.org/10.1186/1471-2288-10-26

[17] Hwang, M.-J., Park, S.Y., Yoon, T.-H., Jang, J., Lee, S.-Y., Yoo, M. *et al.* (2022) Effect of Socioeconomic Disparities on the Risk of COVID-19 in 8 Metropolitan Cities in the Korea: A Community-Based Study. *Epidemiology and Health*, **44**, e2022107. https://doi.org/10.4178/epih.e2022107

[18] McColl, E., Jacoby, A., Thomas, L., Soutter, J., Bamford, C., Steen, N. *et al.* (2001) Design and Use of Questionnaires: A Review of Best Practice Applicable to Surveys of Health Service Staff and Patients. *Health Technology Assessment* (Winchester, England), **5**, 1-256. https://doi.org/10.3310/hta5310

[19] Arashiro, T., Arima, Y., Muraoka, H., Sato, A., Oba, K., Uehara, Y. *et al.* (2022) Behavioral Factors Associated with SARS-CoV-2 Infection in Japan. *Influenza and Other Respiratory Viruses*, **16**, 952-961. https://doi.org/10.1111/irv.12992

[20] Chumakov, K., Avidan, M.S., Benn, C.S., Bertozzi, S.M., Blatt, L., Chang, A.Y. *et al.* (2021) Old Vaccines for New Infections: Exploiting Innate Immunity to Control COVID-19 and Prevent Future Pandemics. *Proceedings of the National Academy of Sciences of the United States of America*, **118**, e2101718118. https://doi.org/10.1073/pnas.2101718118

[21] Ashford, J.W., Gold, J.E., Huenergardt, M.A., Katz, R.B.A., Strand, S.E., Bolanos, J. *et al.* (2021) MMR Vaccination: A Potential Strategy to Reduce Severity and Mortality of COVID-19 Illness. *The American Journal of Medicine*, **134**, 153-155. https://doi.org/10.1016/j.amjmed.2020.10.003

[22] Hassani, D., Amiri, M.M., Maghsood, F., Salimi, V., Kardar, G.A., Barati, O. *et al.* (2021) Does Prior Immunization with Measles, Mumps, and Rubella Vaccines Contribute to the Antibody Response to COVID-19 Antigens? *Iranian Journal of Immunology*, **18**, 47-53.

[23] Noverr, M.C., Yano, J., Hagensee, M.E., Lin, H.-Y., Meyaski, M.C., Meyaski, E. *et al.* (2023) Effect of MMR Vaccination to Mitigate Severe Sequelae Associated With COVID-19: Challenges and Lessons Learned. *Medical Research Archives*, **11**, 3598. https://doi.org/10.18103/mra.v11i2.3598

[24] Shrivastava, J., Narang, M., Ahmed, R.S., Das, S. and Gomber, S. (2023) Serological Response to COVID-19 and Its Association With Measles-Rubella (MR)-Containing Vaccines. *Cureus*, **15**, e39671. https://doi.org/10.7759/cureus.39671

[25] Altulayhi, R.I., Alqahtani, R.M., Alakeel, R.A., Khorshid, F.A., Alshammari, R.H., Alattas, S.G. *et al.* (2021) Correlation between Measles Immunization Coverage and Overall Morbidity and Mortality for COVID-19: An Epidemiological Study. *Environmental Science and Pollution Research International*, **28**, 62266-62273. https://doi.org/10.1007/s11356-021-14980-6

[26] Kolla, E., Weill, A., Desplas, D., Semenzato, L., Zureik, M. and Grimaldi, L. (2022) Does Measles, Mumps, and Rubella (MMR) Vaccination Protect against COVID-19 Outcomes: A Nationwide Cohort Study. *Vaccines*, **10**, Article No. 1938. https://doi.org/10.3390/vaccines10111938