International Journal of Public Health Science (IJPHS)
Vol. 12, No. 1, March 2023, pp. 32~40
ISSN: 2252-8806, DOI: 10.11591/ijphs.v12i1.22470

Vaccination efficacy against post-COVID-19 symptoms in Delta and Omicron waves: a prospective cohort in East Indonesia

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Article Info

Article history:

Received Sep 6, 2022
Revised Nov 3, 2022
Accepted Nov 22, 2022

Keywords:

Delta strain
Indonesia
Omicron strain
Post-COVID-19 symptoms
Vaccination efficacy

ABSTRACT

The post COVID-19 symptoms affect the productivity and the quality of life among survivors. It is imperative to identify the effect of virus variants and the vaccination against post-COVID-19 symptoms. There were 242 participants from the eastern part of Indonesia diagnosed with COVID-19 during July 2021-July to 2022 were recruited online. The participants underwent data collection and semi-clinical follow-up for post-COVID-19 symptoms within 30 days after the first symptoms or from the diagnosis day using a validated clinical questionnaire and physician confirmation. Fatigue was the most reported post-COVID-19 symptom (27.7%), followed by chronic cough (21.5%) and headache (15.3%). Adjusted by confounding factors in hierarchical logistic regression, the differences in post-COVID-19 symptoms were insignificant across different variants. Regarding vaccine efficacy against three post-COVID-19 symptoms, people with two-dose vaccination significantly reported lower post-COVID-19 chronic cough (adjusted Odds Ratio 0.244 95% CI OR 0.071-0.838), but the protection against fatigue and the chronic headache was insignificant. There is an indication that vaccine efficacy may be waning along with the emerging new variants.

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1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrom Coronavirus 2 (SARS-COV2), has become a global threat and affects multiple aspects. The manifestation of COVID-19 is not only limited to the respiratory system but also other system organs, including the nervous system and immune-related manifestation [1]. COVID-19 affects more than 596 million people globally, with 6.5 million fatalities. In South East Asia. Indonesia ranks second after Vietnam, with reported cases of 6.3 million and 157,478 cumulative mortality. Despite a huge target population, the vaccination level for COVID-19 is acceptable, with 74% coverage for the first and 62% for the second. Furthermore, Indonesia has already initiated the first booster for the general population and the second booster [2].

Significant progress in controlling the pandemic has been achieved globally, including implementing boosters, heterologous vaccination, and developing different antivirus. The remarkable change in vaccination is contributed to the reduction of severe cases, particularly the booster vaccination with messenger RNA technology [3]. However, conflicting result is seen in the efficacy of different antivirus, including Favipiravir

and Remdesvir [4]. Furthermore, emerging new variants, including Omicron and its subvariants, lead to a new health burden. Omicron is known for its ability to escape immunity, including the vaccinated people, and higher infectivity. Thus, putting all people at risk of getting infected [5].

Since the probability of people getting an infection remains high, the most critical question is whether the current intervention (vaccination and new medication) is still effective in reducing the severity and whether the people may experience residual symptoms, known as post-COVID-19 symptoms. For example, a study demonstrates persistent symptoms that could last for seven months [6]. Moreover, these post-COVID-19 symptoms affect the quality of life, particularly in particular demographic characteristics and those with severe disease [7].

However, there is limited study on how the different variants affect the occurrence of residual symptoms. For example, a longitudinal study in Indonesia addressed persistent symptoms, including fatigue, chronic cough, and chronic headache within 90 days [8], and the impact of vaccination against specific symptoms, such as olfactory dysfunction [9]. However, these studies did not cover the current period where the Omicron is the most prevalent strain. A systematic review elaborating the effect of vaccination against post-COVID-19 symptoms in three different countries (United Kingdom, United States, and India) shows a conflicting result. Seven studies demonstrated an improvement in long-COVID-19 symptoms when a person received one dose vaccine, although four studies disclosed no change or worsening in long-COVID-19 symptoms after vaccination [10]. Furthermore, most of the studies were retrospective cohort, cross-sectional, and case-control design which exhibit lower evidence.

Assessing the effect of new variants and the vaccination impact on the post-COVID-19 symptoms is imperative. As the level of vaccination is higher compared to the period covered by the previous study, the researchers considered involving participants from the eastern part of Indonesia to cover more unvaccinated people who received the first dose as the level of vaccination in this area is low [11]. Therefore, this study was intended to identify the effect of new variants and vaccination effort against the post COVID-19 symptoms, specifically in eastern part of Indonesia where number of people with vulnerable condition (unvaccinated and partially vaccinated) remains higher.

2. RESEARCH METHOD

2.1. Study design and timeline

This study used a nested cohort of the latest Indonesian post-COVID-19 survey data from July 2021-July 2022, which encompassed the period of Delta and Omicron variants. Furthermore, this research focused on a subset of data from the eastern part of Indonesia as this area is less superior in health infrastructure, particularly procurement of booster shots. Hence this study could address the impact of recent virus strains on post-COVID-19 symptoms in the areas that have not achieved herd immunity.

2.2. Participants and data collection

An online questionnaire with informed consent was disseminated to participants, and the recruitment of participants was based on the snowball technique, referred to by family or colleagues. Assessment of outcomes was conducted on day 30 after onset (or diagnosis day for those who remained asymptomatic). This study did not limit the age. However, online recruitment and the snowball technique might not be feasible to reach younger participants, reducing the generalizability of the findings in the younger population. As for the elderly and those with limited ability to fill in the questionnaire, the survey allows participants to be accompanied by other family members or colleagues when filling in the questionnaire.

Participants were deemed eligible if diagnosed with either a real-time polymerase chain reaction (RT-PCR) test or an antigen test using the nasopharyngeal, nasal, throat swab, or pooled sample of these samples [12]. However, the current regulation of testing does not allow a person to perform self-test antigens for diagnosis, unlike in other countries such as Thailand. Furthermore, the antigen test available in Indonesia should possess a sensitivity of more than 80% and 97% specificity [13]. Participants were excluded for the following reason: people who received prolonged treatment of more than 30 days, those who did not provide the outcome assessment results on day 30, and those with reinfection. However, no specific exclusion was made for people with chronic diseases or other comorbidities.

2.3. Variables

The nested cohort was composed of demographic information, anthropometric measurements, diagnosis methods, vaccination status (including a number of doses and type of vaccine), presence of comorbidities (chronic disease), and health behaviour (including smoking, alcohol drinking, and physical activity), symptoms during COVID-19 (yes or no), treatment (in this case, the prescription of antivirus), and the status of treatment (home isolation, hospitalization, or both). This clinical information was based on daily observations or medical resumes of hospitalized patients.

The researcher defined the severity of the disease according to World Health Organization guidance based on the presence of pneumonia, including oxygen saturation of less than 94%, rapid breathing, or abnormal imaging results [14]. As the genomic sequencing was not feasible, the researcher implemented an approach to presume the possible strain of infection. The study period covered two dominant strains, where from July to December 2021 was the period of Delta, and the initial case of the Omicron variant in December 2021 marked the beginning of the Omicron wave [15]. This study created the binary variable to represent the assumed variant.

2.4. Outcomes

The researcher focused on three long COVID-19 symptoms, fatigue, chronic cough, and headache. All outcomes were assessed using a clinical questionnaire since no specific algorithm or protocol exists to measure the post-COVID-19 symptoms. Hence, the team applied a measurement using validated clinical questionnaires.

This study implemented a measurement outcome using other clinical questionnaires with good specificity and sensitivity. A fatigue severity scale (FSS) questionnaire is a 7-Likert scale with nine questions to distinguish chronic fatigue symptoms that occur as the impact of the disease. Each question has a minimum score of one and a maximum of seven. A cohort in Swiss revealed that a healthy individual had a mean score of 3.00±1.08, which indicates that a mean score above three was defined as fatigue [16]. As for cough and headache, the researchers applied the visual analog scale (VAS), where the minimum score is one and the highest is ten. A score below three indicates mild or no significant disturbing headache [17], whereas in cough, a VAS lower than 40 mm indicates a lower possibility of chronic cough [18]. Through the provided platform enlisted in the questionnaire, participants with any reported post-COVID-19 symptoms underwent confirmation by a physician.

2.5. Sample size

The estimation of sample size was derived from the one sample proportion formula. The researcher selected chronic cough as the primary outcome due to the nature of the SARS-COV2 infection. The initial study demonstrated that the Indonesian population's incidence of chronic cough within 30 days after COVID-19 was 17.3% [8]. With a 95% confidence level, a 5% margin of error, and 10% of non-responsive participants, the estimated sample size was 242.

2.6. Potential bias

The researchers addressed recall bias in certain variables, such as the days of symptoms. For the ease of data collection and analysis, the presence of any symptoms was presented as a binary response. As for vaccination information, the individual data could be retrieved from the PeduliLindungi account.

2.7. Quantification of variables

The researchers preserved continuous data as numbers, including age and body mass index. However, some adjustments were made to specific variables. For example, following the protocol from the survey, antivirus prescription time was described based on the time of diagnosis as <24 hours, 24-72 hours, >72 hours, and not receiving any medication.

There is an assumption that vaccination will not be effective until 14 days [19]. Hence, by estimating the date of vaccination and the day of infection, the researchers discretized the status of vaccination into three levels: i) infected and unvaccinated, ii) infected after receiving one dose or after receiving a second dose less than 14 days (level 1), and iii) infected more than 14 days after the second dose (level 2).

2.8. Statistical analysis

Descriptive statistics elaborated on the characteristic of the participants in the nested cohort, including the prevalence of the selected post-COVID-19 symptoms. Bivariate and subgroup analyses were performed to identify the crude association between the independent factors and post-COVID-19 symptoms. This study estimated the effect of variants and vaccination on post-COVID-19 symptoms using hierarchical logistic regression. The selection of other adjustment factors was based on the crude association of the factors. Moreover, several independent factors may exhibit multicollinearity, which should be omitted from the final model.

2.9. Ethical approval

Following the full board review of the study protocol, a research permit from the Research Ethics Review Committee for Research Involving Human Research Participants of Hasanuddin University was obtained (UH21110687) This study ensured that participants agreed to partake and were aware of future follow-

up. The consent was granted electronically, and all the data was de-identified to maintain confidentiality. Should further information (or immediate care) be required, the participants were allowed to contact the research team for treatment referral.

3. RESULTS

The study involved 242 participants from the eastern part of Indonesia, where the vast majority of them were from Sulawesi (70.2%), Maluku (20.6%), and Papua (9.2%). This cohort's mean age +SD was 32.73±10.65 years, dominated by females (53.3%). One hundred seventy people (70.2%) were infected during the Delta wave, whereas 72 (29.8%) were contracted in the Omicron wave. Most were mild cases (90.1%), followed by moderate (9.1%) and severe cases (0.8%). Average days of treatment ±SD were significantly shorter in those infected during Omicron than in Delta (11.94±3.5 versus 14.92±2.99 days, $p<0.001$). The most reported symptom during infection was fever (93%), cough (86%), and headache (86%).

By calculating the day of infection and the last day of receiving the last dose of vaccine, there were 141 (58.3%) participants who were unvaccinated and contracted COVID-19. Furthermore, 19.5% of participants only received one dose of vaccine or received their second dose but were diagnosed less than 14 days after receiving the second dose. Moreover, those infected more than 14 days after their second dose (fully vaccinated) accounted for 22.2% of the cohort. Regarding the type of vaccine, among 101 people who received the first dose, Sinovac was on the top list (85.1%), followed by AstraZeneca (7.9%), Sinopharm (3%), Pfizer (3%), and Moderna (1%). A similar pattern was also seen in 56 fully vaccinated participants, although the recipient of Sinopharm was the least (1.8%). This study also records two heterologous vaccinations (Sinovac + Astrazeneca and Sinovac + Moderna).

Within 30 days after diagnosis or the first day of the onset, a total of 111 (45.9%) participants reported at least one persistent symptom. Fatigue was reported in 27.7% of participants, followed by chronic cough (21.1%) and chronic headache (15.3%). Table 1 (see in Appendix) describes the characteristic of participants according to the presence of any persistent symptoms within 30 days.

From Table 1 (see in Appendix), demographic and comorbid factors, including health behaviour (smoking, alcohol drinking, exercise), and chronic disease, were not significantly associated with the presence of any post-COVID-19 symptoms within 30 days, except for age, where people who developed residual symptoms were significantly older than those who did not. A shorter duration of treatment was found in those who did not report any residual symptoms. The severity of the disease is also linked to reported symptoms. The researchers also noticed the significant association between variant and vaccination status and reported symptoms. Table 2 depicts the association between variant, vaccination status, and each symptom during the illness.

Table 2. Association between variants, vaccination status, and symptoms

Variables	Variant (Delta as reference)		Vaccination status (Unvaccinated as reference) with 95% CI crude odds ratio	
	Crude odds ratio	p-value	First	Second
Fever	0.580	0.285	0.562 (0.157-2.011)	0.418 (0.134 -1.306)
Myalgia	0.235	<0.001	0.200 (0.081-0.494)	0.241 (0.098-0.590)
Cough	0.359	0.005	0.219 (0.093-0.518)	0.535 (0.206-1.391)
Shortness of breath	0.376	0.001	0.221 (0.107-0.458)	0.306 (0.151-0.621)
Headache	0.201	<0.001	0.132 (0.053-0.327)	0.341 (0.127-0.912)
Sore throat	13.270	<0.001	0.308 (0.136-0.696)	0.058 (0.025-0.131)
Loss of smell	0.237	<0.001	0.199 (0.083-0.048)	0.220 (0.093-0.518)
Runny nose	0.364	0.001	0.480 (0.231-0.998)	0.588 (0.288-1.204)

Notes: Association of variants and symptoms estimated with chi-square, as crude odds ratio of vaccination was estimated with simple logistic regression. The first and second refer to the vaccination level mentioned in the methodology.

Participants reported any symptoms during their COVID-19 episode as a binary response (yes or no), regardless of the duration of the symptoms. According to Table 2, other than fever, people infected during Omicron were less likely to report the symptoms aforementioned during treatment ($p<0.05$). Interestingly, sore throat was more frequent during the Omicron period (<0.001). Full vaccination was crucial in preventing myalgia, shortness of breath, headache, sore throat, and loss of smell (95% confidence interval crude odds ratio shows value lower than 1) during the COVID-19 episode.

Table 3 shows no significant association between the variant and the occurrence of post-COVID-19 fatigue, but not with chronic cough and chronic headache. A similar pattern is also shown in severity and age. However, there was a significant association between vaccination status on the day of diagnosis and all three post-COVID-19 symptoms and the duration of treatment.

The researchers developed two hierarchical models for each symptom to assess the effect of variant and vaccination while accommodating these significant confounders. The first model is the simple model assessing the adjusted effect of variants and vaccination status. Meanwhile, the second is the integration of potential confounders into the final model.

Table 3. Bivariate association of significant predictors with individual post COVID-19 symptoms

Variable	Fatigue	Chronic cough	Chronic headache
Variant	0.062	0.013	0.05
Vaccination status during infected	0.007	<0.001	0.024
Severity*	0.543	0.026	0.074
Age	0.084	<0.001	0.043
Duration of Treatment	<0.001	0.001	0.003

Notes: All categorical variables were tested with Chi-square, except * (Fisher Exact). The association of continuous predictors was estimated with the non-parametric test, while significant at p-value <0.05.

The goodness-of-fit test shows better performance for the second model, except for the first model of fatigue. Nevertheless, interpretation relies on the second model with adjusted factors. Despite insignificant, people infected in the Omicron period were less likely to report post-COVID-19 fatigue (8.7%) and post-COVID-19 chronic cough (17.1%) but not with chronic headaches, where people infected in the Omicron wave were 1,097 times higher than in Delta. Full vaccination status did not provide significant protection for fatigue and chronic headache, but not for chronic cough, with estimated protection of 75.6% (95% CI: 16.2%-92.9%). Longer days of treatment were associated with chronic headache and fatigue but not with chronic cough. Increasing age was also linear to the risk of developing a chronic cough. However, the inverse trend was seen in the occurrence of chronic headaches.

4. DISCUSSION

4.1. Omicron infection was milder than Delta

This study revealed the COVID-19 and post-COVID-19 symptoms in Indonesia's different geographic regions and COVID-19 waves, increasing the information's novelty. Aside from sore throat, prominent in the Omicron period, all other symptoms were more prevalent in the Delta period, and the difference was significant except fever. The United Kingdom's (UK) COVID-19 survey also showed similar findings [20]. Furthermore, people infected during the Omicron period had a shorter treatment duration than Delta. Omicron shows a shorter incubation time [21] and decreased lung infectivity in an in-vivo trial [22]. Hence, the researchers could conclude that Omicron shows a milder impact than Delta.

The previous survey conducted during alpha, beta, and Delta waves showed a similar prevalence of post-COVID-19 symptoms [8]. Fatigue remains the most reported post-COVID-19 symptom in this study and is similar to the reported prevalence in a meta-analysis [23]. Another research pointed out that fatigue was more prevalent in patients admitted to the intensive care unit [24]. In this study, the chronic cough was higher than the chronic headache. The cough hypersensitivity state and neuroinflammatory condition of the vagal sensory nerve stimulate cough in COVID-19 [25]. A study assessing the persistent cough in COVID-19 when the original strain was dominant showed that 20.9% of hospitalized patients had a persistent cough after three weeks [26]. The possible mechanisms of chronic headache in COVID-19 are a direct invasion of SARS-COV2 to the nerve and subsequent injury due to pro-inflammatory mediators and cytokines in the central nervous system [27]. In a multicentric study where the wild-type variant was prevalent, 19% of patients experienced headaches for up to three months [28]. This research showed a lower prevalence of three post-COVID-19 symptoms during the Omicron waves compared to the Delta period as shown in Table 1, indicating a milder effect of Omicron than Delta in terms of the residual symptoms.

4.2. Variant, symptoms, and residual effect

The bivariate analysis showed that all symptoms except fever were significantly different, showing that Omicron shows a lower tendency to develop symptoms than Delta as presented in Table 2, except sore throat. Fever remains a consistent symptom over different variants, despite a decreasing trend in reported fever. A study identified that the odds ratios of fever in Delta and Omicron waves were similar [29]. Regarding post-COVID-19 symptoms, people infected in the Delta waves were more likely to experience chronic cough and chronic headache, but the probability of fatigue was similar between variants as shown in Table 3. There is a limited peer-reviewed study concerning this issue. However, a pre-print of a study in Norway showed a different finding that chronic cough is similar in two variants [30].

Demographic factors did not play a significant role in post-COVID-19 symptoms. The risk of developing post-COVID-19 symptoms within 30 days was similar in terms of occupation, health behaviour, and the presence of chronic disease, although, in the final model as shown in Table 4, older age was associated with post-COVID-19 chronic headache and chronic cough. However, a large-scale study of non-hospitalized patients shows contrary findings where women, young people, smokers and patients with comorbidities were prone to any post-COVID-19 symptoms [31]. There was no significant difference in all post-COVID-19 symptoms regarding the Favipiravir prescription. Favipiravir shows low clinical improvement, thus providing insignificant protection for residual symptoms [4].

Table 4. The hierarchical model of post COVID-19 symptoms

Variable	Model 1			Model 2		
	B	Odds ratio	95% CI odds ratio	B	Odds ratio	95% CI odds ratio
Model for post-COVID-19 fatigue						
Omicron variant (Delta Ref)	-0.371	0.690	0.272-1.751	-0.091	0.913	0.352-2.368
Unvaccinated (ref)						
The first dose, or <14 days after the second dose	-0.269	0.764	0.27-2.164	0.025	1.025	0.352-2.984
Infected >14 days after the second dose	-1.16	0.313	0.127-0.776	-0.709	0.492	0.192-1.261
Duration of Treatment (in days)				0.198	1.219	1.081-1.374
Hosmer Lemeshow p-value			0.829			0.085
Model for post-COVID-19 chronic cough						
Omicron variant (Delta Ref)	-0.025	0.975	0.332-2.862	-0.187	0.829	0.265-2.600
Unvaccinated (ref)						
The first dose, or <14 days after the Second Dose	-1.532	0.216	0.055-0.852	-0.79	0.454	0.106-1.935
Infected >14 days after the second Dose	-1.694	0.184	0.059-0.573	-1.412	0.244	0.071-0.838
Duration of Treatment (in days)				0.05	1.051	0.922-1.199
Mild severity (Ref)						
Moderate				0.919	2.507	0.889-7.072
Severe				1.29	3.633	0.174-75.844
Age in years				0.085	1.089	1.051-1.128
Hosmer Lemeshow p-value			0.757			0.967
Model for post-COVID-19 chronic headache						
Omicron varian (Delta Ref)	-0.224	0.799	0.248-2.578	0.092	1.097	0.329-3.658
Unvaccinated (ref)						
The first dose, or <14 days after the Second Dose	-1.161	0.313	0.068-1.442	-1.378	0.252	0.053-1.209
Infected >14 days after the second Dose	-0.86	0.423	0.146-1.231	-0.602	0.548	0.178-1.685
Duration of Treatment (in days)				0.182	1.2	1.038-1.388
Age in years				-0.06	0.942	0.904-0.981
Hosmer Lemeshow p-value			0.329			0.561

A simple crosstabulation pointed out crude protection of having at least one dose against the presence of symptoms (except fever) compared to unvaccinated in the overall cohort. However, full vaccination did not show consistent efficacy as full vaccination did not significantly prevent fever, cough, and runny nose as presented in Table 2. Nevertheless, vaccination still benefits in preventing three post-COVID-19 symptoms as shown in Table 3, although this is only a crude effect.

To accommodate the confounding effect, the researcher applied logistic regression to assess the impact of SARS-COV2 variants and vaccination on the selected post-COVID-19 symptoms. In post-COVID-19 fatigue, adjusted by the duration of treatment, people infected during the Omicron period were less likely to develop fatigue, although it was not significant. Furthermore, insignificant protection was also seen in those fully-vaccinated individuals infected more than 14 days after their second dose as presented in Table 4.

There was no significant difference in chronic headache between variants, adjusted by age and duration of treatment. The same finding also occurred in the full vaccination status. Interestingly, adjusted by age, treatment duration, and disease severity, full vaccination shows a 75.6% protection against chronic cough as shown in Table 4. However, this study had an inconsistent effect of being partially vaccinated against post-COVID-19 symptoms. A large community study recorded a higher reduction of post-COVID-19 after receiving the first dose (12.8%) compared to the second dose (8.8%) [32].

The possible explanation for why people with full vaccination status have low protection against post-COVID-19 symptoms is that the efficacy of vaccination decrease over time [33]. People may get infected after certain months of full vaccination. This study did not calculate the days between the last dose and infection and treated it as continuous data when considering the vaccination effect. Furthermore, access to booster vaccination remains limited in this study area.

Another issue is that these inconsistent findings were probably due to methodology. Although there was a limitation involving heterogeneous participants such as vaccination type (as Sinovac recipients dominate this nested cohort), most of the participants were recruited during the Delta period, and there was lower

recruitment for those who were unvaccinated. People may now be more reluctant to report themselves to the health provider, thus reducing the recruitment of participants at the current time. Regarding data management, a potential bias should be considered, such as the days of treatment. The World Health Organization defined a protocol for isolation and treatment [34]. However, the current definition seems to be heterogenous across time, such as released by antigen results or the 5+5 rules. Thus, the duration of treatment has potential measurement bias. Currently, there are no COVID-19-specific measurements of the post-COVID-19 outcome. However, the measurement tools used in this study are the tools that are currently being assessed by the post-COVID-19 core outcome Set study, which reduces the measurement bias in outcome assessment [35]. Lastly, the researchers also acknowledge that assuming the type of variants according to the date of infection is not equivalent to genomic sequencing.

5. CONCLUSION

Despite the limited methodology, this study addressed a new finding that the Omicron shows milder clinical manifestation than Delta variants, although there was no difference in post-COVID-19 symptoms within 30 days. However, the researchers also acknowledge that the efficacy of vaccination against post-COVID-19 symptoms was not consistent compared to the previous study, except for preventing chronic cough. Nevertheless, it is still essential to increase the accessibility of vaccination, including boosters in low-resource settings such as Eastern Indonesia, to reduce the non-health burden due to post-COVID-19 symptoms.

ACKNOWLEDGEMENTS

The researchers thank Khairun University, Hasanuddin University, and Chulalongkorn University for the research collaboration. The funder of this sub-site study, Khairun University, has no role in the study design, data collection, analysis, decision to publish, or manuscript preparation. This nested study is part of registered study NCT05060562 on the US clinical trials website.

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Appendix

Table 1. Characteristic of participants and reported persistent symptoms within 30 days

Variable	Subset	Reporting at least one persistent symptom within 30 days		p-value
		No (%)	Yes (%)	
Age (year)	Mean (standard deviation)	31.43+10.78	34.26+10.33	0.017
Body mass index (kg/m2)	Mean (standard deviation)	22.89+3.99	23.45+5.16	0.751
Sex	Female	69 (53.5)	60 (46.5)	0.830
	Male	62 (54.9)	51 (45.1)	
Occupation	Medical personnel	45 (59.2)	31 (40.8)	0.283
	Non-medical personnel	86 (51.8)	80 (48.2)	
Education level	Junior high school	2 (100)	0 (0)	0.222#
	Senior high school	30 (54.5)	25 (45.5)	
	Diploma	33 (45.8)	39 (54.2)	
	Bachelor's degree and graduate level	66 (58.4)	47 (41.6)	
Hypertension	No/unknown	122 (54.2)	103 (45.8)	1.000#
	Yes, controlled	5 (55.6)	4 (44.4)	
	Yes, uncontrolled	4 (50.0)	4 (50.0)	
Diabetes	No/unknown	125 (55.1)	102 (44.9)	0.201#
	Yes, controlled	1 (16.7)	5 (83.3)	
	Yes, uncontrolled	5 (55.6)	4 (44.4)	
Smoking status	No	117 (52.5)	106 (47.5)	0.075
	Yes	14 (73.7)	5 (26.3)	
Alcohol consumption	No	122 (52.8)	109 (47.2)	0.059
	Yes	9 (81.8)	2 (18.2)	
Moderate exercise/week	>3 times per week	23 (69.7)	10 (30.3)	0.111
	2-3 times per week	31 (56.3)	24 (43.7)	
	1 or less per week	77 (50.0)	77 (50.0)	
Vaccination status during infected	The first dose, or <14 days after the second dose	32 (68.1)	15 (31.9)	<0.001
	Infected >14 days after the second dose	41 (75.9)	13 (24.1)	
	Unvaccinated	58 (41.1)	83 (58.9)	
Favipiravir administration	<24 hours after diagnosis	18 (58.1)	13 (41.9)	0.292
	24-72 hours after diagnosis	15 (53.5)	13 (46.5)	
	>72 hours after diagnosis	5 (31.2)	11 (68.8)	
	Not receiving any treatment	93 (55.7)	74 (44.3)	
Severity	Mild	125 (57.3)	93 (42.7)	0.006#
	Moderate	6 (27.3)	16 (72.7)	
	Severe	0 (0)	2 (100)	
Variant	Delta	83 (48.8)	87 (51.2)	0.011
	Omicron	48 (66.7)	24 (33.3)	
Duration of treatment	Mean (standard deviation)	12.94+3.61	15.32+2.69	<0.001

Notes: All categorical variables were tested with Chi-square, except # (Fisher Exact). The association of continuous predictors was estimated with the non-parametric test, while significant at p-value <0.05.