ORIGINAL ARTICLE

Level of SARS-CoV-2 exposure post the CoronaVac vaccination in health workers at Dr. Saiful Anwar General Hospital, Malang

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ABSTRACT

Introduction: COVID-19 is considered a new emerging infection due to SARS-CoV-2. CoronaVac refers to an inactivated SARS-CoV-2 vaccine obtaining EUL (Emergency use listing) from BPOM RI and WHO. This vaccine was previously reported to exhibit good efficacy in generating protective antibodies against SARS-CoV-2. Nevertheless, health workers in Indonesia might pose a high risk of COVID-19 exposure, leading to mortality. This study aims to identify the level of SARS-CoV-2 exposure to the CoronaVac vaccination in health workers at Dr. Saiful Anwar General Hospital, Malang.

Methods: This study implemented analytical observational research with a prospective cohort approach on health workers at Dr. Saiful Anwar General Hospital, Malang, who received the 2nd dose of vaccination dose with a 14-day interval. All study subjects were observed for 6 months by examining the level of exposure to SARS-CoV-2 obtained from the results of nasopharyngeal and oropharyngeal swab examinations of SARS-CoV-2 RT PCR examination. Categorical data were tested by using Chi-square or Fisher exact.

Results: From 184 samples, the SARS-CoV-2 exposure indicated several outcomes: positive 57 (31 %) and negative 127 (69%). Severity degrees of COVID-19 disease were asymptomatic 17 (29.8%), mild 37 (64.9), moderate 3 (5.3%), severe 0 (0%), and there were no mortality cases. The time (duration) of exposure to SARS-CoV-2 post-CoronaVac vaccination indicated that the highest number of participants with positive RT-PCR swab results post-vaccination was in the fifth month of the CoronaVac vaccination with 41 people. Clinical symptoms of SARS-CoV-2 exposure experienced by participants post the CoronaVac vaccination included pneumonia (3 people), cough and cold (27 people), fever (22 people), myalgia (17 people), and sore throat (11 people). There was no significant relationship p value > 0.05 between gender, age, comorbidities, and Ct value on SARS-CoV-2 exposure post CoronaVac vaccination in health workers at Dr. Saiful Anwar General Hospital, Malang.

Conclusion: There was SARS-CoV-2 exposure of 31% post the CoronaVac vaccination in health workers at Dr. Saiful Anwar General Hospital, Malang.

INTRODUCTION

COVID-19 is a new emerging infectious disease due to SARS-CoV-2, primarily affecting the lower respiratory tract, experienced by all age populations. The main transmission of this disease is navigated through droplet splash when an infected person sneezes/coughs, transmitting directly to other individuals or indirectly through contamination of surface objects. This transmission causes the disease to spread rapidly from one person to another.[1] Symptoms that arise if infected vary from asymptomatic fever, cough, runny nose, and headache to shortness of breath, such as pneumonia, ARDS, multiorgan function failure, and even mortality.[2] The onset of pneumonia, severe symptoms, and death due to COVID-19 are associated with the presence of comorbidities experienced by patients, including old age, diabetes mellitus, hypertension, and cardiovascular disease.[3]

Vaccination is regarded as one of the most critical efforts to control infectious diseases, including COVID-19, expected to generate herd immunity, thereby mitigating the incidence of SARS-CoV-2 infection. In addition, vaccination also is expected to prevent pneumonia and other severe symptoms of SARS-CoV-2 infection, thus minimizing the potential for hospitalization.[1,2] CoronaVac (Sinovac Life Sciences, Beijing, China) refers to an inactivated SARS-CoV-2 vaccine obtaining Emergency use listing by BPOM RI and WHO and is the first vaccine purchased by the Indonesian government given to priority groups, including health workers. The results of preclinical trials indicated good immunogenicity in mice and non-human primates with vaccine-induced neutralization to SARS-CoV-2.[4] The results of phase 3 clinical trials in several countries, including Indonesia, indicated an efficacy of 65.7% post

receiving 2 doses, postulating that this vaccine could prevent infection in people compared to those who received a placebo. From the results of these clinical trials, it is apparent that groups who have received the CoronaVac vaccine might still be exposed to COVID-19 but with mild and asymptomatic clinical manifestations, which could minimize the need for hospitalization.[4,5]

According to data on the number of health workers in East Java Province until the end of July 2021 who have received CoronaVac vaccination (131,997 people), the number of vaccinated health workers in Malang was 12.521 people; meanwhile, at Dr. Saiful Anwar General Hospital, the number of health workers who have received a complete dose of vaccination is 6052 people. Although individuals have been vaccinated, the incidence of post-vaccination COVID-19 infection might still have the potential to occur. This probability is due to differences in the immune response in each individual and the challenge of the mutation of SARS-CoV-2 generating higher virulence than the wild-type variant.[6] Hence, this study aims to identify the level of SARS-CoV-2 exposure to the CoronaVac vaccination in health workers at Dr. Saiful Anwar General Hospital, Malang

METHODS

This study is categorized as an observational analytic study with a prospective cohort approach. The study duration was initiated after receiving the 2nd vaccination dose in February 2021 to the 6th month of August 2021. The 1st dose of CoronaVac vaccination was conducted in mid-January 2021, while the 2nd dose was performed in February 2021 with an injection interval of 14 days post the admission of 1st dose.

The selection of research samples was conducted by implementing the simple random sampling method based on the database from P-Care indicating data on individual subjects vaccinated at Dr. Saiful Anwar General Hospital. The research sample included in this study comprised an affordable population that fulfilled the inclusion criteria (had received CoronaVac vaccination for 2 doses in 2x admissions, aged 18-60 years. COVID-19 diagnosis

was confirmed based on the results of PCR examination inside and outside RSSA, CT value RT-PCR was obtained from the RSSA microbiology laboratory) and exclusion criteria (autoimmune patients and gravida). All participants included in this study were asked to sign an online informed consent sheet via Google form. The study was conducted post obtaining approval from the ethics committee of Dr. Saiful Anwar General Hospital Malang.

All baseline data were collected by filling out an online questionnaire, which included age, gender, health worker profession, comorbid history, and questionnaire for the presence of symptoms of infection or exposure to SARS-CoV-2 post-vaccination if symptoms were reported. An RT-PCR examination of SARS-CoV-2 then followed it. Furthermore, participants were observed until the end of the six-month study period for 6 months to determine whether they were confirmed for COVID-19. Symptomatic and asymptomatic participants were caught tracing from health workers who were positive for RT-PCR SARS-CoV-2 at week 1 to 23 post-vaccination, while nasopharyngeal and oropharyngeal swabs were undertaken for RT-PCR SARS-CoV-2 examination. Meanwhile, participants were asymptomatic until the end of the study period and were not confirmed positive when tracing progressed into nasopharyngeal and oropharyngeal swabs for SARS-CoV-2 PCR examination at week 24.

Further, the collected data were recorded in a logbook and continued to statistical analysis at the end of data collection. Statistical tests were performed, including descriptive analysis and correlation tests. Categorical data were tested by using Chi-square or Fisher exact. All statistical tests were performed with the SPSS 25.0 program for Windows, depicting a p-value of <0.05, considered significant.

RESULTS

Based on patient data collected, it was found that 194 samples met the inclusion and exclusion criteria of the study. The research sample that did not follow the tracing until the end of the study period

was 10 people, generating a research sample that could be analyzed comprising 184 people. The characteristics of the participants are illustrated in Table 1.

SARS-CoV-2 exposure post the CoronaVac vaccination for 6 months was found in 57 participants from the total (n-184), occurring more in women (30 people (16.30%)) than in men (27 people (14.70%)), with age range of 21-30 years (21 people (11, 40%)) and 31-40 years (27 people (14.70%)) who were more exposed than the elderly, the PPDS profession was more exposed (45 people (24.50%) than Supervisors (5 people (2.7%)) and nurses (7 people (3.8%)), with mild cases of COVID-19 (37 people (20. 10%)), and asymptomatic cases (17 people (9.20%)) were more common in study subjects exposed to SARS-CoV-2 than moderate degree (3). There were no cases of severe degree and death. In addition, the CT value of RT-PCR successfully obtained was 17 out of 57 participants exposed to SARS-CoV-2. This finding was because CT Value was only obtained from RT-PCR sample processing at the RSSA Microbiology Lab. (Table 2).

The results indicated that the study subjects who were exposed to SARS-CoV-2 post the CoronaVac vaccination included those with no comorbidities (31 people (16.80%)), compared to those with comorbidities (26 people (14.10%)). The comorbidities that most people were exposed to SARS-CoV-2 post-vaccination included asthma, dyslipidemia, and hypertension.

Post conducting the Chi-square / Fisher exact test to assess the relationship between variables, this study did not find a relationship among age, gender, health worker profession, and comorbidities with SARS-CoV-2 exposure the CoronaVac vaccination (p>0.5), and there was no relationship found between CT value and severity of COVID-19 disease. Meanwhile, the relationship between the severity of COVID-19 disease and exposure to SARS-CoV-2 post the CoronaVac vaccination in health workers at Dr. Saiful Anwar Malang was significant (p<0.5).

Based on the length of time (duration) of exposure to SARS-CoV-2 post the CoronaVac vaccination, the highest number of participants with positive RT-

Table 1. Data Characteristics of Participants (n=184)

Variables		result
Age (years)	Mean ± SD	35±9.0
	Ages range	26-58
	21-30	75 (40.8%)
	31-40	71 (38.6%)
	41-50	24 (13.0%)
	51-60	14 (7.6%)
Sex	Men	80 (43.5%)
	Women	104 (56.5%)
Profession	Specialist doctors	27 (14.7%)
	Nurse	33 (17.9%)
	Resident	124 (67.4%)
Comorbid	None	99 (55%)
	Comorbid	85 (45%)
	- Hypertension	30
	- Asthma	29
	- Dyslipidaemia	13
	- Obesity	8
	- Allergies	5
	- Diabetes	5
	- Tuberculosis	4
	- Heart disease	4
	- Others	5
SARS-CoV-2 exposure	Positive	57 (31%)
	Negative	127 (69%)
Severity of COVID-19	Asymptomatic	17 (29.8)
	Mild	37 (64.9)
	Moderate	3 (5.3%)
	Severe	0 (0%)
	Critical	0 (0%)
CT Value RT-PCR	≤ 20	11 (64.7%)
	>20	6 (35,5%)
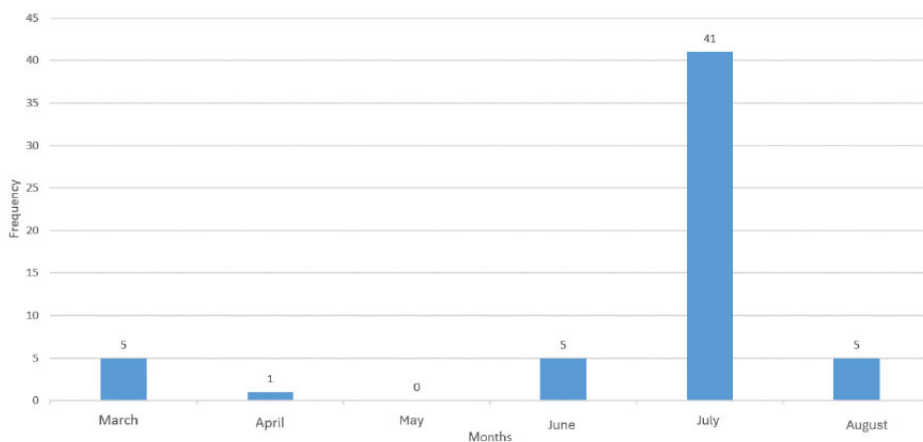
Figure 1. The number of subjects with positive PCR swab results post-vaccination is based on the time post the CoronaVac vaccination.

PCR swab results post-vaccination was in the 5th month or in July post the CoronaVac vaccination with 41 people, and the lowest number was in May (0 people). In addition, March, June, and August had similar numbers of participants with positive RT-PCR swab results post-vaccination (Fig.1)

During the study period of 6 months, there were 3 participants exhibiting comorbidity (2 people) and non-comorbidity (1 person) groups experiencing a moderate degree of illness when infected with COVID-19 post-CoronaVac vaccination, required for

hospitalization, and there was no severe degree of illness found until the mortality. The most common clinical symptoms of COVID-19 were cough and cold, followed by fever (22 people), myalgia (17 people), sore throat (11 people), anosmia (7 people), ageusia (5 people), nausea and vomiting (4 people), diarrhea (4 people), pneumonia (3 people), and headache (1 people).

In this study we also established the relationship among gender, age, degree of illness, and profession of the study subjects with exposure to SARS-CoV-2 post the CoronaVac vaccination. In this study, we found that only the severity of COVID-19 was significantly associated with SARS-CoV-2 exposure to the CoronaVac vaccination.

Most patients with positive SARS-CoV-2 exposure had no comorbid (16.80%). The most comorbid in this study was asthma (8,23%). In addition, we found no significant relationship between comorbidity the SARS-CoV-2 exposure to the CoronaVac vaccination (p=0.916). The detailed description is provided in Table 3.

DISCUSSION

The results of this study found that the CoronaVac vaccine could protect approximately 69% of health workers at Dr. Saiful Anwar Malang General Hospital from exposure to SARS-CoV-2, which the findings of this study are in line with prior studies conducted in the population in Indonesia and other countries when CoronaVac phase 3 clinical trials were conducted. The interim analysis of the phase 3 clinical study was conducted in Indonesia (as of January 8, 2021) involving 1,620 general population adult subjects aged between 18-60 years. The interim analysis of efficacy was conducted based on the cut-off date of January 8, 2021, with a total of 25 COVID-19 cases (as specified in the protocol for target cases at least exhibiting 60% VE up to 90 days post the second injection) which was 65.3%.[7] However, the findings of this study are not in line with the study conducted by Can Gunay et al. (2022) in Turkey, which assessed the relationship between CoronaVac vaccination and COVID-19 infection in health workers at Istanbul University Hospital in determining the

effectiveness of the vaccine on 4067 health workers who were followed up with PCR starting post 14 days after receiving the second dose of CoronaVac vaccination. The real-life study conducted on the study subjects indicated that the effectiveness of two doses of the CoronaVac vaccine (39%) was lower than clinical trials which were conducted in several countries due to the decreasing protection of antibodies

produced by the CoronaVac vaccine over time, in addition to the transmission of the Gamma Variant of Concern out breaking at the time the study, thereby triggering the immune to escape; thus that the incidence of infection or reinfection occurs in people who have been vaccinated. As such, WHO recommends the admission of a booster dose injection.[8]

This study found that the highest

number of health workers exposed from June to August post-vaccination was 41 people, which could be related to the outbreak of the SARS-CoV-2 delta variant in Malang City. This finding is based on the WGS COVID-19 examination report of Dr. Saiful Anwar General Hospital for 9 samples of the confirmed COVID-19 patients undergoing treatment in the COVID-19 isolation room on August 14, 2021, released by BALITBANGKES, from which 8 of the 9 patient samples were confirmed positive for SARS-CoV-2 Variant of concern Delta. The effect of the delta variant during our study period indicated an increase in transmission and a decrease in the response of neutralizing antibodies obtained through vaccination or natural infection. However, our study subjects primarily exposed indicated mildly symptomatic and asymptomatic.

Comorbid variables in our study indicated no significant relationship between comorbidity and exposure to SARS-CoV-2, the CoronaVac vaccination (p=0.916). However, exposure to SARS-CoV-2 in health workers in the non-comorbid group was found to have a more significant percentage than the comorbid group, even though it was not statistically significant. This presentation could be due to a decrease in neutralizing antibodies that have been formed post-vaccination over
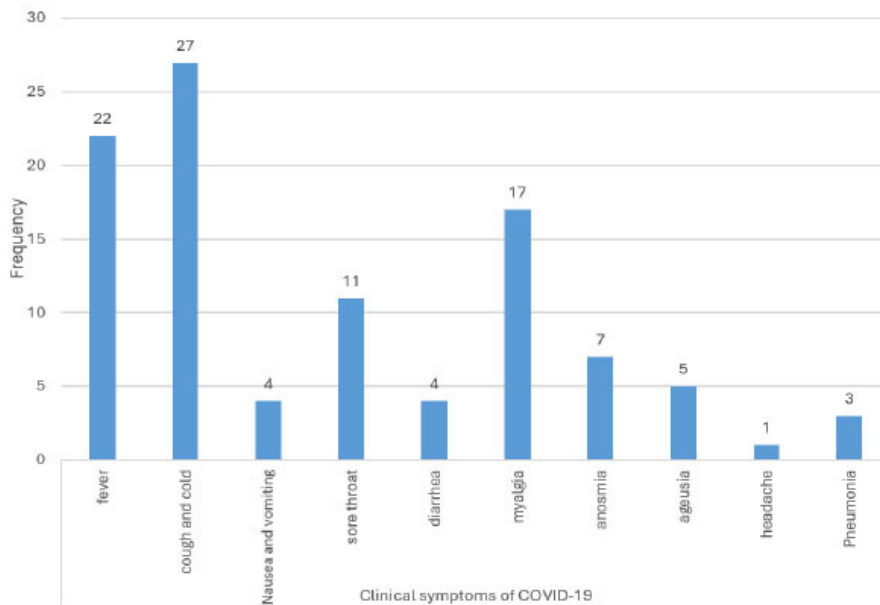
Figure 2. Clinical symptoms of COVID-19 infection experienced by participants post the CoronaVac vaccination.

Table 2. Relationship among gender, age, degree of illness, and profession of the study subjects with exposure to SARS-CoV-2 post-CoronaVac vaccination

Variables		SARS-CoV-2 Exposure				Total		P-Value
		Negative		Positive				
		n	%	n	%	n	%	
Gender	Women	74	40.20	30	16.30	104	56.50	
	Men	53	28.80	27	14.70	80	43.50	0.476
	Total	127	69.00	57	31.00	184	100.00	
Age (years)	21-30	54	29.30	21	11.40	75	40.80	
	31-40	44	23.90	27	14.70	71	38.60	0.281
	41-50	17	9.20	7	3.80	24	13.00	
	51-60	12	6.50	2	1.10	14	7.60	
	Total	127	69.00	57	31.00	184	100.00	
Severity of COVID-19	Asymptomatic	127	69.00	17	9.20	144	78.30	
	Mild	0	0.00	37	20.10	37	20.10	0.000*
	Moderate	0	0.00	3	1.60	3	1.60	
	Total	127	69.00	57	31.00	184	100.00	
Professions	Residents	79	42.90	45	24.50	124	67.40	
	Doctor specialist	22	12.00	5	2.70	27	14.70	0.079
	Nurses	26	14.10	7	3.80	33	17.90	
	Total	127	69.00	57	31.00	184	100.00	

*Significant p-value (p<0.05)

Table 3. Relationship between comorbidities and SARS-CoV-2 exposure post the CoronaVac vaccination

Comorbid	SARS-CoV-2 Exposure				Total		P Value
	Negative		Positive				
	n	%	n	%	n	%	
None	68	37.00	31	16.80	99	53.80	0.916
Comorbid type	59	32.10	26	14.10	85	46.20	
- Asthma			7	8,23			
- Dyslipidaemia			5	5,88			
- Hypertension			3	3,52			
- Tuberculosis			3	3,52			
- Heart disease			2	2,35			
- Obesity			1	1,17			
- Inflammatory bowel disease			1	1,17			
- Rhinitis vasomotor			1	1,17			
- COPD			1	1,17			
- HT+DM			1	1,17			
- ASMA+TB			1	1,17			
Total	127	69.00	57	31.00	184	100.00	

time, where several journals have reported a decrease in antibodies in the period of > 6 months post-vaccination, theoretically indicating to be more dominant in the comorbid group. However, in this study, the non-comorbid group had more exposure because the number of research samples in the non-comorbid group was more significant than the comorbid group. In addition, there was a SARS-CoV-2 mutation included in the delta variant of concern during the study period resulting in increased transmission and a significant decrease in neutralizing antibodies produced in response to vaccination. According to Bilgin et al. (2022), the decrease in neutralizing antibodies post the CoronaVac vaccination could be due to plasma blasts (CD19+CD138+) as plasma cell precursors and LLPCs (Long-life plasma cells) were responsible for antibody production remaining detectable in the peripheral blood. This presentation raises the possibility that these cells have not fully moved from the peripheral blood to the lymph nodes and have not yet reached the germinal centre reaction phase, which is required for humoral immunity and leads to the maturation of immunoglobulin affinity and B lymphocyte proliferation.[9] However, from the non-comorbid group, one research subject exhibited a moderate degree of disease, while 2 research subjects indicated a moderate degree of disease in the comorbid group. This presentation indicates that the comorbid group has the potential to develop the severity of

COVID-19 disease when exposed to SARS-CoV-2 post-vaccination.[10]

The results of this study indicated no significant relationship between gender and exposure to SARS-CoV-2, the CoronaVac vaccination (p=0.476). This finding follows a study conducted by Can Gunay et al. (2022) in Turkey, which assessed the relationship between CoronaVac vaccination and COVID-19 infection in health workers at Istanbul University Hospital, emphasizing that SARS-CoV-2 infection detected from men and women groups had a non-meaningful relationship (p = 0.890).[8] However, in this study, women exhibited more SARS-CoV-2 exposure presentations (16.30%) than men (14.70%) due to the higher number of women (56.50) compared to men (43.50%) study subjects. In studies conducted by Scully et al. (2021), gender differences in terms of confirmed SARS-CoV-2 infection depend on age in all countries, where it is greater in women aged between 10-50 years than in men before the age of 10 years and post the age of 50 years.[11] Meanwhile, in this study, the research subjects who had a severe degree of disease, as many as 3 people were found in men. This presentation is consistent with global data indicating that sex-based differences exist in the clinical outcomes of COVID-19, with men being more affected by early SARS-CoV-2 infection, hospitalization, and poor clinical outcomes. In addition, the theory has been presented previously that

men have risk factors for experiencing COVID-19 with a more severe degree of disease than women.[12] According to prior studies by Scully et al. (2021) and Kopel et al. (2020), in comparison to males, women showed superior antibody production and response. They were also less prone to viral infection, produced less cytokines, had better neutrophil and macrophage activity, and produced more antibodies overall.[11,13] Both basal immunoglobulin levels, equivalent to antibody responses to vaccines, were reported to be consistently higher in women than men.[11]

Our results in the age group variable indicated no significant relationship to SARS-CoV-2 exposure with a p-value = 0.281. However, the most exposure to SARS-CoV-2 post the CoronaVac vaccination was experienced in the 31-40 years age group for 27 people (14.70%), followed by the 21-30 years age group for 21 people (11.40%), the 41-50 years age group for 7 people (3.8%), and the 51-60 years age group for 2 people (1.10%). According to the previous concept respiratory infections might be induced by immunosenescence in the elderly, which resulted in decreased mucosal barriers, mucociliary clearance, immunological response, and respiratory tract inflammation against pathogenic microorganisms.[14] As cilia in the upper respiratory tract become fewer in number and less active, the mucociliary clearance mechanism is diminished. Reduced IgA in the nasal mucosa and lungs can also lead to a reduced ability of the respiratory system

to neutralize viral infections. However, in this study, the research objects of 31-40 years old and 21-30 years experienced the most post-vaccination SARS-CoV-2 exposure compared to those above age. This is possible because, at the age of over 20 years, most of the subjects of this study were PPDS, who became the first-line health workers directly dealing with the confirmed and probable COVID-19 patients at Dr. Saiful Anwar General Hospital.[8,15]

Statistical analysis of the type of profession of health workers on exposure to SARS-CoV-2 indicated no relationship between the profession of health workers and exposure to SARS-CoV-2 (p=0.079). However, the results of this study indicated that the most exposure to SARS-CoV-2 post the CoronaVac vaccination was experienced in the resident / PPDS health worker group of 45 people (24.50%), followed by nurses of 7 people (3.80%). This is possible because PPDS became the first-line health workers directly dealing with the confirmed and probable COVID-19 patients at Dr. Saiful Anwar General Hospital. Furthermore, the habit of gathering among PPDS colleagues for various activities and applying suboptimal health protocols has resulted in PPDS being potentially exposed to SARS-CoV-2 post-vaccination.

The findings of the statistical analysis in this research showed that the known CT-value for the severity of COVID-19 illness had a p-value = 0.624 for 17 health professionals at Dr. Saiful Anwar General Hospital, Malang. The link between CT-value results and clinical outcomes has not been fully recognised. The association between CT-value readings and hospitalisation, illness severity, and death was shown in a systematic review research conducted by Shah et al. (2021) in patients who were older than 18 and had been exposed to SARS-CoV-2. There was no discernible difference in the mean CT-value results of hospitalised and non-hospitalized individuals, according to a meta-analysis of seven studies. In hospitalised patients, there was a significant difference in the chances of more severe illness and death between those with CT values <25 and >30 ([OR: 2.31; 95% CI: 1.70 to 3.13, and OR: 2.95;

95%CI: 2.19 to 3.96, respectively). Patients with CT values of 25–30 showed a lower probability of worsening illness severity and mortality when compared to those with values >30. Three investigations showed no correlation between the severity of the illness and the CT value, while two other studies showed no statistical significance. This presentation raises the prospect of varying outcomes in terms of the correlation between the CT value and the severity of the illness in various locations.[16]

The limitation of the study were this study was only conducted in one center, this design study was a cross-sectional study, therefore the data collection only at one particular time. For the further research we suggest changing the study design thus that data can be taken at certain times, thereby a trend in post-vaccination COVID-19 infection can be performed.

CONCLUSIONS

The incidence of SARS-CoV-2 exposure was found with 31% with asymptomatic, mild, and moderate degrees of illness post the CoronaVac vaccination in health workers at Dr. Saiful Anwar General Hospital, Malang. The findings of this study indicated that there was no relationship among age, gender, profession, and comorbidity with SARS-CoV-2 exposure post the CoronaVac vaccination at Dr. Saiful Anwar General Hospital Malang, and there was also no relationship between CT Value on RT-PCR examination and severity of COVID-19 disease post the CoronaVac vaccination at Dr. Saiful Anwar General Hospital, Malang.

DISCLOSURES

Funding
None.

Conflict of Interest
Regarding this publication, none of the writers has any conflicts of interest to disclose.

Author Contribution
Each author made an equal contribution to this research.

Ethics Approval
The ethical commission of Dr. Saiful Anwar General Hospital, Malang, had ethically approved this study.

REFERENCE

1. Burhan E, Susanto S, Nasution S, Ginanjar. E, Pitoyo C, Susilo A. Protokol Tatalaksana Pasien Terkonfirmasi Covid-19. 4th ed. Jakarta; 2020. 1–149 p.
2. Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Herikurniawan H, et al. Coronavirus Disease 2019: Tinjauan Literatur Terkini. Jurnal Penyakit Dalam Indonesia. 2020;7(1):45.
3. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069–76.
4. WHO. Evidence Assessment: Sinovac/CoronaVac COVID-19 vaccine. SAGE Working Group on COVID-19 vaccines. 2021. p. 1–32.
5. BPOM. FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF CORONAVAC. 2021 Aug.
6. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181–92.
7. WHO. Annexes to the recommendations for use of the Sinovac-CoronaVac vaccine against COVID-19: Grading of evidence, Evidence to recommendation tables. 2021. p. 1–50.
8. Can G, Acar HC, Aydin SN, Balkan II, Karaali R, Budak B, et al. Waning effectiveness of CoronaVac in real life: A retrospective cohort study in health care workers. Vaccine. 2022;40(18):2574–9.
9. Bilgin H, Marku M, Yilmaz SS, Karahasan Yagci A, Sili U, Can B, et al. The effect of immunization with inactivated SARS-CoV-2 vaccine (CoronaVac) and/or SARS-CoV-2 infection on antibody levels, plasmablasts, long-lived-plasma-cells, and IFN-γ release by natural killer cells. Vaccine. 2022;40(18):2619–25.
10. Zhang J, Dong X, Liu G, Gao Y. Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality. Clin Rev Allergy Immunol. 2022;64(1):90–107.
11. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020;20(7):442–7.
12. Raza HA, Sen P, Bhatti OA, Gupta L. Sex hormones, autoimmunity and gender disparity

in COVID-19. Rheumatol Int. 2021;41(8):1375–86.

13. Kopel J, Perisetti A, Roghani A, Aziz M, Gajendran M, Goyal H. Racial and Gender-Based Differences in COVID-19. Front Public Health. 2020;8.

14. Murray MA, Chotirmall SH. The Impact of Immunosenescence on Pulmonary Disease. Mediators Inflamm. 2015;2015:1–10.

15. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. New England Journal of Medicine. 2021;385(16):1474–84.

16. Shah VP, Farah WH, Hill JC, Hassett LC, Binnicker MJ, Yao JD, et al. Association Between SARS-CoV-2 Cycle Threshold Values and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2021;8(9).