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The role of COVID-19 survivor status and gender towards neutralizing antibody titers 1, 2, 3 months after Sinovac vaccine administration on clinical-year medical students in Indonesia

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ABSTRACT

Background: Sinovac was the first vaccine used in Indonesia against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, data regarding the effects of certain variables such as clinical demographics on antibody levels in individuals vaccinated with Sinovac are scarce. This study aimed to investigate the impact of gender and previous SARS-CoV-2 infection status on neutralizing antibody titers 1, 2, and 3 months after administration of the Sinovac vaccine.

Method: A cross-sectional study was conducted from February to May 2021. Data on neutralizing antibody levels, previous SARS-CoV-2 infection status, and gender were retrieved from the monthly quantitative serology evaluation database of Siloam Hospitals Lippo Village, Tangerang, Indonesia. The role of each variable was analyzed using the *t*-test or Mann-Whitney U test, depending on data distribution.

Result: Data from 350 participants were collected for the study. Participants with a history of a positive SARS-CoV-2 RT-PCR test had significantly higher neutralizing antibody titers in the first (144 U/mL, $p = 0.036$) and second months (144 U/mL, $p = 0.005$) after vaccination compared with those without a history of positive RT-PCR test. Female participants also had significantly higher neutralizing antibody titers in the first, second, and third months (43 U/mL, 42 U/mL, and 39 U/mL, respectively; $p = 0.001$, $p = 0.002$, and $p = 0.003$, respectively) after vaccination compared to males.

Conclusion: COVID-19 survivor status and the female gender were associated with higher neutralizing antibody titers after Sinovac vaccine administration.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been actively circulating and causing disease for over a year

(Jalkanen et al., 2021). In Indonesia, the first case of coronavirus disease 2019 (COVID-19) was confirmed on March 2, 2020, and the virus has rapidly spread since then, disrupting multiple aspects of life, including healthcare, such as by hindering routine childhood immunizations due to limited health services (Fahrhani et al., 2021). With the increasing incidence of SARS-CoV-2 infection, a high prevalence of long COVID-19 and its consequences has also been reported (Fahrhani et al., 2021; Yusuf et al., 2021). Several treatment agents have also been investigated to manage COVID-19

Abbreviation: COVID-19, Coronavirus Disease 2019.

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patients and reduce its mortality burden (Hariyanto et al., 2021a; Hariyanto et al., 2021b; Hariyanto et al., 2021c).>).

To alleviate the impact of SARS-CoV-2 in Indonesia, the government began a COVID-19 Vaccination Program on January 13, 2021, which was split into four phases (Amira, 2021). The first phase prioritized healthcare workers and the vaccine was CoronaVac, a COVID-19 vaccine produced by Sinovac Life Sciences, Beijing, China. Various studies have been conducted on the safety and efficacy of the Sinovac vaccine (Tanriover et al., 2021; Zhang et al., 2021); however, data regarding the effect of different variables, such as gender and COVID-19 survivor status, on the antibody titers induced by this vaccine are scarce, and no data were found regarding Indonesia. A previous study reported that males are at a higher risk of poor prognosis and severe COVID-19 outcomes, while previous SARS-CoV-2 infections have a protective effect against re-infection (Vahidy et al., 2021; Vitale et al., 2021). Thus, this study aimed to investigate the effect of COVID-19 survivor status and gender on neutralizing antibody titers 1, 2, and 3 months after Sinovac vaccine administration.

Material and methods

A cross-sectional study was conducted between February and May 2021. Clinical-year students of the Faculty of Medicine at Pelita Harapan University who had undergone a quantitative serology test were selected by convenience sampling from the student database. Their data were then collected from the Siloam Hospitals Lippo Village database. All clinical-year students at the Faculty of Medicine, Pelita Harapan University having data from an IgG serology test, specifically to the S1 subunit (receptor binding domain) conducted via electrochemiluminescence immunoassay (ECLIA; measured in U/mL) and a recorded COVID-19 survivor status were included. COVID-19 survivor status was defined as any previous infection with SARS-CoV-2 before the first dose of vaccination, confirmed by a positive reverse transcription-polymerase chain reaction (RT-PCR) result. No particular exclusion criteria were used. All study participants were vaccinated with the first dose of

the Sinovac vaccine on February 5, 2021, with the second dose administered on February 19, 2021, as part of the mandatory vaccination program. Data on neutralizing antibody titers, COVID-19 survivor status, and gender were collected from the monthly quantitative serology evaluation database of Siloam Hospitals Lippo Village on March 4 and 5 for the first month, April 5 and 6 for the second month, and May 5 and 6 for the third month after vaccination.

Statistical analysis was performed using IBM SPSS 26.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). The *t*-test or Mann-Whitney U test was used, depending on the distribution of data, to evaluate the neutralizing antibody titers each month in relation to COVID-19 survivor status and gender. This study was ethically approved by The Ethics Committee of Faculty of Medicine, Pelita Harapan University with ethics number 085/K-LKJ/ETIK/II/2021.

Results

Data were gathered from a total of 350 participants on 1, 2, and 3 months after the administration of the Sinovac COVID-19 vaccine. Table 1 shows participants' characteristics. The median neutralizing antibody titer after vaccination was 40 (1-250) U/mL in the first month, 40 (0-250) U/mL in the second month, and 36 (0-1051) U/mL in the third month. Most participants were female (70%, 71%, and 66%, respectively) and the majority did not have a history of SARS-CoV-2 infection (95%, 95%, and 98%, respectively). The Mann-Whitney U test of the relationship between COVID-19 survivor status and neutralizing antibody titers (Table 2) showed a significantly higher titer during the first and second months after vaccination in those with history of SARS-CoV-2 infection, compared with those without a history of SARS-CoV-2 infection (144 U/mL vs 40 U/mL for the first month, 144 U/mL vs 40 U/mL for the second month), while no significant difference was seen in the third month. Analysis of the relationship between gender and neutralizing antibody titers (Table 3) yielded significantly higher titers in females every month compared to males (43 U/mL vs 29 U/mL for the first month, 42 U/mL vs 39 U/mL for the second month, and

Table 1
Demographics of participants.

Variable	1 month post vaccine (n=350)	2 months post vaccine (n=279)	3 months post vaccine (n=138)
	n (%)		
Gender			
Female	243 (70)	197 (71)	91 (66)
Male	107 (30)	82 (29)	47 (34)
History of SARS-CoV-2 infection			
No	331 (95)	266 (95)	135 (98)
Yes	19 (5)	13 (5)	3 (2)
Median age (range)	22 (19-28)	22 (20-25)	22 (20-26)

Table 2
Mann-Whitney U test analysis of COVID-19 survivor status with neutralizing antibody titers at 1, 2, 3 months after vaccine, based on COVID-19 survivor status.

History of SARS-CoV-2 infection	Antibody titers 1 st month		Antibody titers 2 nd month		Antibody titers 3 rd month	
	Median (Min-Max)	p-value	Median (Min-Max)	p-value	Median (Min-Max)	p-value
No	40 (1-248)	0.036	40 (0-183)	0.005	36 (0-1051)	0.051
Yes	144 (39-250)		144 (39-250)		143 (37-250)	

Table 3
Mann-Whitney U test analysis of COVID-19 survivor status with neutralizing antibody titers at 1, 2, 3 months after vaccine, based on gender.

Gender	Antibody titers 1 st month		Antibody titers 2 nd month		Antibody titers 3 rd month	
	Median (Min-Max)	p-value	Median (Min-Max)	p-value	Median (Min-Max)	p-value
Female	43 (3-250)	0.001	42 (0-250)	0.002	39 (0-1051)	0.003
Male	29 (1-234)		39 (4-183)		29 (3-108)	

39 U/mL vs 29 U/mL for the third month). Higher neutralizing antibody titers were seen in females and participants with a history of SARS-CoV-2 infection.

Discussion

This study found that neutralizing antibody titers were 2–4 times higher in the first two months after vaccine administration in participants with a previous SARS-CoV-2 infection. These results are similar to those of a study that assessed antibody responses in seropositive individuals after a single dose of the SARS-CoV-2 vaccine (Krammer et al., 2021), which found that the antibody titers of vaccinees with pre-existing immunity were higher than those of individuals without pre-existing immunity after a single dose of Pfizer and Moderna vaccines. A study assessing SARS-CoV-2 antibody responses in individuals with past infection also reported that significantly lower neutralizing antibody titers were found in patients without a history of SARS-CoV-2 infection (Anichini et al., 2021).

The current study also found that female participants had significantly higher neutralizing antibody titers in all three months after vaccination, as stated in another study that compared SARS-CoV-2 IgG antibody levels in males and females and found that female participants generated higher antibody counts compared with male participants (Zeng et al., 2020); however, the exact cause of this gender-based difference is unknown.

The current study was limited by the low number of participants with a history of COVID-19; this may explain why the analysis of COVID-19 survivor status in relation to neutralizing antibody titer in the third month after vaccination yielded an insignificant result, despite having a similar difference in median values to the first two months between those with and without a history of SARS-CoV-2 infection. It was also unable to analyze other variables, due to limited data availability in the database. Future studies should ensure a better distribution of study participants and analysis of other variables. Despite these limitations, it is believed that this study is the first to compare neutralizing antibody titers across three months after COVID-19 vaccination and thus provides valuable information to determine which group should be prioritized for further vaccine shots or booster shots.

Conclusions

COVID-19 survivor status and female gender affected neutralizing antibody titers after COVID-19 vaccination, with significantly higher antibody levels in the first two months post-vaccination in individuals with a history of SARS-CoV-2 infection and in females in all three months post vaccination. Further studies are needed to confirm these results.

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Declaration of competing interest

None.

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Ethical approval statement

This study has been ethically approved by The Ethics Committee of Faculty of Medicine, Pelita Harapan University with ethics number 085/K-LKJ/ETIK/II/2021.

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