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ASSOCIATION BETWEEN COVID-19 VACCINATION STATUS WITH SEVERITY OF CONFIRMED COVID-19 PATIENTS PERIOD OF JANUARY-JULY 2022 IN INDONESIA

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ABSTRACT

The COVID-19 vaccine is known to prevent infection, disease severity, and death from COVID-19. The emergence of a new variant of the SARS-CoV-2 would have an impact on the vaccine's effectiveness. This study aims to examine the association between COVID-19 vaccination status and the severity of COVID-19 symptoms during the dominating period of the Omicron variant. This is a cross-sectional study using secondary data from confirmed COVID-19 patients who were reported in the Ministry of Health's Online Hospital System for the period January–July 2022. Using logistic regression analysis, we calculated the adjusted odds ratio (AOR) of the association between vaccination status and the severity of COVID-19 symptoms. A total of 221,673 confirmed COVID-19 patient data were analyzed. The proportion of patients with severe-critical symptoms is 6.25%. Multivariate analysis showed there was a statistically significant association between COVID-19 vaccination status and the severity of COVID-19 disease with an AOR 0.73 (95% CI 0.65-0.82) in the 1st dose, 0.38 (95% CI 0.35-0.41) at the 2nd dose, and 0.09 (95% CI 0.07-0.11) at the 3rd dose. But the magnitude of the association in the 2nd and 3rd was lower in the age group ≥60 years, the group with comorbidities, and the male sex group compared to the younger age group, those without comorbidities, and the female group. It can be concluded that COVID-19 vaccination reduces the risk of severity of COVID-19 disease. Government acceleration efforts and public awareness are needed to immediately increase the coverage of the booster dose of vaccination. Further prospective studies are needed to monitor the effectiveness and duration of vaccine protection as other new variants of the SARS-CoV-2 virus emerge.

Keywords: *COVID-19, vaccination, effectiveness, severity, omicron*

ABSTRAK

Vaksin COVID-19 diketahui dapat mencegah infeksi, keparahan penyakit hingga kematian pada penderita COVID-19. Munculnya varian baru SARS-CoV-2 dikhawatirkan mempengaruhi efektifitas vaksin. Studi ini bertujuan untuk melihat hubungan antara status vaksinasi COVID-19 dengan keparahan gejala COVID-19 pada periode mendominasinya varian Omicron. Studi dengan disain *cross sectional* ini menggunakan data sekunder pasien konfirmasi COVID-19 yang dilaporkan dalam sistem RS Online Kementerian Kesehatan periode Januari-Juli 2022. Dengan menggunakan regresi logistik, kami menghitung *adjusted odds ratio* (AOR) hubungan status vaksinasi dengan keparahan gejala COVID-19. Total 221.673 data pasien terkonfirmasi COVID-19 dianalisis. Proporsi pasien COVID-19 bergejala berat-kritis adalah 6,25%. Analisis multivariat menunjukan ada hubungan yang bermakna secara statistik antara status vaksinasi COVID-19 dengan keparahan penyakit COVID-19 dengan nilai AOR 0,73 (95% CI 0,65-0,82) pada dosis pertama; 0,38 (95% CI: 0,35-0,41) pada dosis kedua dan 0,09 (95% CI 0,07-0,11) pada dosis ketiga. Tetapi besar asosiasi pada vaksin dosis dua dan tiga terlihat lebih rendah pada kelompok usia ≥60 tahun, kelompok yang memiliki komorbid, dan kelompok jenis kelamin laki-laki dibandingkan dengan kelompok usia yang lebih muda, tidak memiliki komorbid dan kelompok perempuan. Dapat disimpulkan vaksinasi COVID-19 mengurangi risiko keparahan penyakit COVID-19. Diperlukan upaya akselerasi pemerintah maupun kesadaran masyarakat untuk segera meningkatkan cakupan vaksinasi *booster*. Selain itu diperlukan studi prospektif lebih lanjut untuk memantau efektifitas dan durasi perlindungan vaksin seiring munculnya varian baru virus SARS-CoV-2 lainnya.

Kata kunci: COVID-19, vaksinasi, efektifitas, keparahan, omicron

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Introduction

Corona Virus Disease (COVID-19) was first discovered in December 2019 in Wuhan, China, and was declared as Pandemic by WHO in March 2020. COVID-19 is still a health problem at the global level now, including in Indonesia.[1] In Indonesia, until December 2022, confirmed cases of COVID-19 had reached more than 6.7 million cases, with deaths reaching more than 160 thousand cases.[2] The clinical manifestations of COVID-19 vary from asymptomatic to severe/critical symptoms. In severe cases, patients can experience Acute Respiratory Distress Syndrome (ARDS), resulting in multi-organ failure and death.[1,3,4]According to data, in countries affected early in the pandemic, 15% of cases experience severe symptoms, and 5% of cases are in critical condition.[5] Older people, male, and people with pre-existing medical conditions are at greater risk of experiencing severe COVID-19 symptoms.[6,7]

One of the efforts to prevent severe symptoms and death from COVID-19 is the COVID-19 vaccination, which began in Indonesia in January 2021. The cytopathic effect of the virus and its ability to defeat the immune response are factors in the severity of the viral infection. An inadequate immune system in responding to infection determines the severity of symptoms; on the other hand, an excessive immune response can also play a role in tissue damage.[8] The initial functional antibody response within the first 14 days of symptoms correlates with the severity and likelihood of disease recovery. Delayed humoral immunity is evident in the more severe and lethal COVID-19. This indicates the importance of achieving strong pre-immunity through vaccination before being infected with COVID-19.[9]

The impact of vaccination in preventing infection, severity, and death of COVID-19 has been proven in vaccine effectiveness studies that have been carried out in various countries with various types of COVID-19 vaccines.[10,11]The results of a meta-analysis of 51 studies showed that two doses of COVID-19 vaccination provided protection of 89.1% against infection, 97.2% against hospitalization, 97.4% against ICU care and 99% against death.[10]In Indonesia, until December 2022, around 74% of vaccination targets had received the primary COVID-19 vaccination (two doses), and around 29% had received the third dose of vaccination.[12]On the other hand, there is concern that the existence of a new variant of the SARS-CoV-2 virus would affect the effectiveness of the vaccine.[13]

Studies assessing the effectiveness of vaccines on the severity of COVID-19 disease in Indonesia, especially during the circulation period of the Omicron variant, were still limited. For this reason, this study aimed to assess the impact of vaccination in preventing COVID-19 with severe-critical symptoms. This study used data on confirmed cases of COVID-19 from January to July 2022, where during this period, the transmission of COVID-19 was dominated by the Omicron

variant.[14] It was hoped that the results of this study could be used as evaluation material for control efforts of COVID-19, especially the COVID-19 vaccination program in Indonesia.

Methods

A cross-sectional study design was used in this research by using secondary data from the Ministry of Health's Online Hospital information system for the period of January - July 2022. The Online Hospital information system was an application developed to report individual data on COVID-19 patients from all hospitals in Indonesia. The inclusion criteria were cases of COVID-19 with positive RT-PCR laboratory results reported in the online hospital system and at least 18 years of age. Exclusion criteria were confirmed cases of COVID-19 with incomplete measured variable data, variable data of vaccines with non-plausible vaccination dates (the vaccination dates were the same between doses 1 and 2 and 3), as well as respondents who used vaccine types that were not used in Indonesia until July 2022 (vaccine used in Indonesia: Sinovac, Moderna, Pfizer, AstraZeneca, Sinopharm, Covovax-Novavax and Johnson&Johnson).

Figure 1 describes the study population and sampling. Of the total 351,292 population confirmed cases of COVID-19 for the January-July 2022 period reported in the online hospital system, 306,081 were aged >18 years (87.13%). From these, 84,105 (23.94%) did not have complete data, 133 (0.04%) used vaccine types that were not used in Indonesia, and 170 (0.05%) had non-plausible vaccine date data, so there were 221,673 (63.1%) confirmed cases that met the inclusion and exclusion criteria (eligible). Out of 221,673, there were 89,208 respondents who had not been vaccinated and as many as 132,465 respondents who had been vaccinated, and all of them were taken as samples.

The variable severity of symptoms in the COVID-19 case was obtained from the online hospital system, which was filled in by hospital staff based on criteria set by the Ministry of Health. Severity levels included asymptomatic, mild, moderate, severe, and critical. The criteria for mild symptoms were patients with confirmed COVID-19 accompanied by mild symptoms and no clinical signs of pneumonia or hypoxia; moderate symptoms were patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) without signs of severe pneumonia with an oxygen saturation of >93%; Severe symptoms were patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) plus one of respiratory rate > 30 x/minute or severe respiratory distress and oxygen saturation <93%, while critical symptoms were patients with COVID-19 with severe pneumonia and using a ventilators.[15,16]In this study, the severity of symptoms were divided into two categories, asymptomatic-moderate symptoms, and severe-critical symptoms.

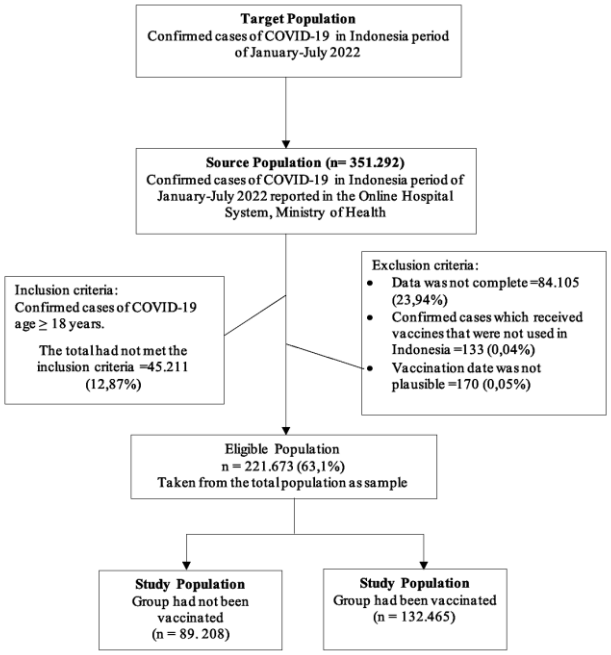

Figure 1. Study Population and Sampling

Vaccination variables in the form of the number of doses, date of vaccination, and type of vaccine were also obtained from the online hospital system, which was integrated with the Vaccination P-Care system. The operational definition of vaccination status was the number of vaccine doses received by a confirmed case of COVID-19 before the date of admission to the hospital and categorized as unvaccinated, dose 1, dose 2, and dose 3 (booster). Other variables that were seen and suspected as confounders or effect modifiers were age (categorized as <60 years and >60 years), gender (categorized as female and male), comorbid status (categorized as having no comorbidities and having at least one comorbid such as heart disease, diabetes, hypertension, obesity, cancer, etc.), and domicile origin (categorized outside Java Island and Java Island).

Univariate analysis was carried out to find out the description of each variable. The association between vaccination status and the severity of COVID-19 symptoms in crude form and adjusted odds ratio (OR) was calculated using logistic regression analysis with 95% confidence intervals. Adjusted OR was estimated from a model that included confounding variables and interaction variables. A variable was said to be a confounder if the difference in the OR in the reduced and full models in multivariate analysis is >10%. Before evaluating the confounding variables, a multivariate analysis was carried out to see if there was an interaction between vaccination status and the age group variable; comorbid status; and gender; if the p-value <0.05, then there was an interaction and the interacting variables must be entered into the model. If there was evidence of an interaction, the magnitude of association between vaccination status and the severity of symptoms was stratified based on other interacting variables. Further analysis was

carried out in the subgroups that had been completely vaccinated with the primary (two doses) and the third dose compared to the unvaccinated group, but the observed vaccination status changed according to vaccine type. The formula (1-AOR)*100% can be used to calculate the vaccine effectiveness.[17]Data analysis was performed by STATA software version 14.1. This research has received approval from the Ethics Committee of the Faculty of Public Health, University of Indonesia, with a certificate of ethical approval number Ket-675/UN2.F10.D11/PPM.00.02/2022.

Results

Table 1. The Characteristics of Respondents and Bivariate Analysis of Factors Associated with the Severity of Symptoms of Confirmed Cases of COVID-19

Variable	n (%)	COVID-19 symptom severity		p-value	Crude OR (95% CI)
		Asymptomatic-Moderate n (%)	Severe-critical n (%)		
	221.673	207.813 (93,75%)	13.860 (6,25%)	-	-
Age (mean + SD)	46,14 ± 18,07	45,18 ± 11,88	60,48 ± 7,78	-	1,05 (1,047-1,05)
Age group					
<60 years	162.581 (73,34%)	156.612 (96,33%)	5.969 (3,67%)	<0,001	1
≥60 years	59.092 (26,66%)	51.201 (86,65%)	7.891 (13,35%)		4,04 (3,9 – 4,19)
Gender					
Female	125.068	118.812 (95%)	6.256 (5%)	<0,001	1
Male	96.605 (43,58%)	89.001 (92,13%)	7.604 (7,87%)		1,62 (1,57 –1,68)
Comorbid Status					
No comorbid	184.662 (83,3%)	178.080 (96,44%)	6.582 (3,56%)	<0,001	1
Having comorbid	37.011 (16,7%)	29.733 (80,34%)	7.278 (19,66%)		6,62 (6,39 - 6,86)
Origin					
Outside Java Island	66.219 (29,87%)	62.702 (94,69%)	3.517 (5,31%)	<0,001	1
Java Island	155.454 (70,13%)	145.111 (93,35%)	10.343 (6,65%)		1,27 (1,22 –1,32)
Vaccination Status					
Not vaccinated	89.208 (40,24%)	80.482 (90,22%)	8.726 (9,78%)	<0,001	1
1st Dose	16.433 (7,41%)	15.323 (93,25%)	1.110 (6,75%)		0,67 (0,63 -0,71)
2nd Dose	83.212 (37,54%)	79.631 (95,70%)	3.581 (4,30%)		0,41 (0,40–0,43)
3rd Dose	32.820 (14,81%)	32.377 (98,65%)	443 (1,35%)		0,13 (0,11 - 0,14)

The number of confirmed cases of COVID-19 period of January-July 2022 included in this study was 221,673, with the proportion of respondents experiencing COVID-19 with severe-critical symptoms of 6.25%. The description or characteristics of research respondents can be seen in table 1. The average age of the respondents was 46.14 (SD + 18.07) years, with 73.34% of the respondents being <60 years old. As many as 56.42% of respondents were female, 83.3% had no comorbidities, and 70.13% lived on Java Island. Respondents who had not been vaccinated at all were 40.24%, and the rest had been vaccinated with details of 7.41% of the first dose of vaccination, 37.54% of the second dose of vaccination, and 14.81% of the third dose of vaccination (booster). Based on the frequency distribution of the independent variable on the severity of symptoms, the majority of confirmed cases of COVID-19 with severe-critical symptoms were in the group who had not been vaccinated at all, were >60 years old, had at least one co-morbidity, were male and domiciled in Java. Based on bivariate analysis, vaccination status, and other covariate variables had a statistically significant association with the severity of COVID-19 symptoms (p-value <0.001). (Table 1)

Based on the evaluation of the interaction of variables in the multivariate analysis, it was known that the age, comorbid status, and gender group variables interact with vaccination status, thereby modifying the magnitude of the association of vaccination status with the severity of COVID-19 symptoms (Table 2). Meanwhile, based on the confounding evaluation, it was known that the variables of age and comorbid status were confounding variables. The domicile variable was not a confounder, so it was not included in the multivariate model. Therefore, the final model for multivariate analysis was a model that includes vaccination status, age group, gender, comorbid status, and interaction variables (Table 2). From the final multivariate analysis model, it was known that there was an association between vaccination status and the severity of COVID-19 symptoms which had been adjusted (adjusted OR). There was a statistically significant association between vaccination status and the severity of COVID-19 symptoms, and this association showed a dose-response relationship. The vaccinated group had a lower risk of developing severe-critical COVID-19 than the unvaccinated group with AOR 0.73 (95% CI 0.65-0.82) at the first dose; AOR 0.38 (95% CI: 0.35-0.41) at the second dose and AOR 0.09 (95% CI 0.07-0.11) at the third dose. It could also be interpreted that vaccination reduced the risk of COVID-19 severity by 27% at the first dose, 62% at the second dose, and 99.91% at the third dose (Table 2).

Table 2. The Results of Multivariate Analysis of the Association Between COVID-19 Vaccination Status and Symptoms Severity of Confirmed Cases of COVID-19

Variable	β (Coef)	p-value	Adjusted OR	95% CI
Vaccination Status				
Not vaccinated	-	-	1	-
1st Dose Vaccination	-032	<0,0001	0,73	(0,65-0,82)
2nd Dose Vaccination	-0,98	<0,0001	0,38	(0,35-0,41)
3rd Dose Vaccination	-2,38	<0,0001	0,09	(0,08-0,11)
Age group				
<60 years	-	-	1	-
≥60 years	0,73	<0,0001	2,08	(1,99-2,18)
Comorbid status				
No comorbid	-	-	1	-
Having comorbid	1,37	<0,0001	3,93	(3,74-4,11)
Gender				
Female	-	-	1	-
Male	0,26	<0,0001	1,29	(1,23-1,35)
Vaccine & Age Interaction				
Vaccine 1*age	-0,084	0,233	-	-
Vaccine2*age	0,29	<0,0001	-	-
Vaccine 3*age	0,48	<0,0001	-	-
Vaccine & Comorbid Interaction				
Vaccine 1*comorbid	-0,008	0,907	-	-
Vaccine 2*comorbid	0,39	<0,0001	-	-
Vaccine 3*comorbid	0,80	0,001	-	-
Vaccine & Gender Interaction				
Vaccine 1*gender	0,21	0,002	-	-
Vaccine 2*gender	0,15	<0,0001	-	-
Vaccine 3*gender	0,37	<0,0001	-	-

Because the age, comorbid status, and gender group variable modify the effect of vaccination status on the severity of COVID-19 symptoms, the adjusted OR was calculated for each of these strata. The negative (protective) association between vaccination status and the severity of COVID-19 symptoms and the dose-response relationship was still consistently seen in each stratum. However, the magnitude of the association was lower in the age group >60 years, with comorbidities, and men compared to those who were younger, without comorbidities, and women. The difference in the magnitude of the association was more visible in the second and third doses of vaccination (Table 3).

Table 3. The Association between Vaccination Status and Severity of COVID-19 Symptoms Based on Age Group, Comorbid Status, and Gender

	1st Dose of Vaccination		2nd Dose of Vaccination		3rd Dose of Vaccination	
	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
Age group						
<60 years	<0,001	0,72 (0,65-0,82)	<0,001	0,38 (0,35-0,41)	<0,001	0,09 (0,08 -0,11)
≥60 years	<0,001	0,67 (0,58–0,77)	<0,001	0,50 (0,46-0,55)	<0,001	0,15 (0,12-0,19)
Comorbid status						
No Comorbid	<0,001	0,73 (0,65-0,82)	<0,001	0,38 (0,35-0,41)	<0,001	0,09 (0,08-0,11)
Having	<0,001	0,72 (0,62-0,84)	<0,001	0,56 (0,51-0,61)	<0,001	0,21 (0,16-0,27)
Gender						
Female	<0,001	0,73 (0,65-0,82)	<0,001	0,38 (0,35-0,41)	<0,001	0,09 (0,08-0,11)
Male	0,109	0,90 (0,80-1,02)	<0,001	0,44 (0,40-0,47)	<0,001	0,13 (0,11-0,16)

**Odds ratios* adjusted for age, comorbid, gender, and interaction variables

Further analysis was carried out to see the relationship between vaccination status by type of vaccine and the severity of COVID-19 in the group that received the second and third doses of vaccination (Table 4). Respondents who received the Covovax-Novavax and Johnson&Johnson vaccines were not included in the analysis because their numbers were small. The five types of vaccines analyzed showed lower effectiveness in the second dose compared to the effectiveness of the third dose of vaccine. The vaccine that had the highest effectiveness against the severity of COVID-19 was Sinopharm in the second dose of vaccination and Moderna in the third dose of vaccination.

Table 4. The Association between Vaccination Status Based on Vaccine Type and Severity of COVID-19 Symptoms in Groups of Recipients of the Second and Third Doses of Vaccine

Type of Vaccine	2nd Dose Vaccination			3rd Dose of Vaccination **		
	Number of respondents with severe-critical symptoms/total	p-value	Adjusted OR* (95% CI)	Number of respondents with severe-critical symptoms/total	p-value	Adjusted OR* (95% CI)
Not vaccinated	8.726/89.208 (9,78%)		1			1
Sinovac	2.869/63.421 (4,52%)	<0,001	0,57 (0,55-0,60)	2/221 (0,9%)	0,004	0,13(0,03 -0,52)
Sinopharm	40/3.373 (1,19%)	<0,001	0,22 (0,16-0,30)	4/504 (0,79%)	<0,001	0,13 (0,05-0,35)
Astrazenaca	385/10.544 (3,65%)	<0,001	0,55 (0,49-0,61)	148/6.354 (2,33%)	<0,001	0,29 (0,25-0,34)
Moderna	42/1.553 (2,7%)	<0,001	0,43 (0,32-0,59)	84/16.585 (0,51%)	<0,001	0,10 (0,08-0,12)
Pfizer	238/4.280 (5.56%)	<0,001	0,68 (0,59-0,74)	204/9.150 (2,23%)	<0,001	0,25 (0,22-0,29)
Covovax	0/3 (0%)	-	-	0/1 (0%)	-	-
Johnson& Johnson	7/38 (18,42%)	-	-	1/5 (20%)	-	-

*Odds ratios adjusted for age, comorbid, gender, and interaction variables

** The type of third dose vaccine without considering the type of primary dose vaccine

Discussion

This study aimed to assess at the impact of the COVID-19 vaccination on the severity of COVID-19 symptoms in the January-July 2022 period, which was the period when the Omicron variant dominated in Indonesia. In this study, it was found that the overall effectiveness of the COVID-19 vaccine against severe-critical COVID-19 was 62% (95% CI 59% -64%) in the second dose and 99.91% (95% CI 99.97% - 99.89%) on the third dose. The results of this study were in line with a study in Qatar which assessed the duration of protection and effectiveness of an mRNA-based vaccine against Omicron infection with severe-critical symptoms that showing the effectiveness of the second dose of vaccine ranged from >60% and >70% and administration of the third dose increased vaccine effectiveness to >80%.[18]The results of this study also appeared to be consistent with a study conducted in January-April 2022 in Thailand which showed the third and fourth doses of the ChAdOx1 nCoV-19 vaccine and mRNA could provide high protection against the severity of COVID-19 disease around 87% to 100%, while the second dose of vaccination provided a moderate level of protection (70%).[19]

The effectiveness of the second dose of vaccine obtained from this study was lower when compared to the results of a meta-analysis of vaccine effectiveness studies recruited in August-October 2021 which showed the effectiveness of the second dose of vaccine against ICU admission was 97.4% (95% CI 96, 0–98.8%).[10]Another study in Sweden showed that the effectiveness of the second dose of vaccine against the severity of COVID-19 decreased from 89% on days 15-30 to 64% on days 121 and beyond.[20]A systematic review concluded that the effectiveness of the vaccine against hospitalization and death from severe COVID-19 disease decreased slowly after the scheduled second dose of the COVID-19 vaccine.[21]Based on the results of this study and supported by several other studies, the second dose of vaccination alone was not sufficient to provide protection against the severity of COVID-19 and a booster dose of vaccination was needed to provide a higher level of protection. Unfortunately, this writing was written (in December 2022), and the coverage of the third dose of vaccination nationally was only around 29%.[12]

The study results showed that there were differences in vaccine effectiveness based on age group, comorbid status, and gender. Vaccine effectiveness in the age group >60 years was lower than in the younger age group. This result was in line with the study by Andrew et al. (2022), which assessed the duration of protection of the BNT162b2 and ChAdOx1-S vaccines against mild and severe COVID-19 symptoms, which showed that the age group >65 years had lower vaccine effectiveness and this effectiveness tended to decline faster, compared to the younger age group.[22]A possible explanation for this was that with age, the competence of the immune system decreased due to degeneration of the entire innate and adaptive immune system.[23]These findings supported the Indonesian government's policy of first giving a second booster (fourth dose) for the elderly age group (> 60 years).

The effectiveness of vaccines on the severity of COVID-19 also appeared to be lower in groups with at least one comorbid disease. These results were supported by other studies which showed that the effectiveness of vaccines in people who had comorbidities was lower and decreased more quickly than in groups who did not have comorbidities.[22,24]A systematic review stated that chronic diseases such as diabetes, hypertension, and cardiovascular disease were the most common comorbidities found in COVID-19 patients. In people who had co-morbidities that were chronic in nature, there would be a decrease in the competence of the immune response, so they were more easily infected by COVID-19 and could experience a bad outcome.[25]This study also showed that the effectiveness of the vaccine in men was slightly lower than in women. Compared to men, women were known to develop faster and stronger innate and adaptive immune responses. This difference in immune response was related to hormonal and genetic factors related to gender. The hormone estrogen, which was more in women, increased the immune response, while the hormone testosterone tended to weaken the immune response. In addition, in women, there were two X chromosomes which contain genes that function in terms of immunity.[26]

In this study, the proportion of COVID-19 with severe-critical symptoms was 6.25%. This proportion was lower than the results of a meta-analysis of 212 studies at the start of the pandemic, which recorded a proportion of COVID-19 with severe-critical symptoms was 23%.[27]The lower proportion of COVID-19 with severe-critical symptoms might be due to several things; most people already had immunity (antibodies) obtained either through vaccination or natural infection.[28] Or there was a change in the effect of a new variant of the SARS-COV-2 virus in causing disease severity. [29]

This research was a cross-sectional study using a large number of samples. To the best of the researchers' knowledge, previous studies in Indonesia that assessed the impact of vaccination on the severity of COVID-19 were still limited, especially during the period when the Omicron variant dominated. The validity of the vaccination status data was considered high because it was taken from the P-Care Vaccination application, which was integrated with the Online Hospital. There were several limitations in this research. First, this study uses secondary data that came from hospital reporting. There was a possibility that hospital staff input incorrectly or did not update patient condition data in the online hospital system application. However, this limitation had been minimized with technical guideline for filling in the RS Online system and routine data verification. Second, researchers cannot obtain information regarding disease progression from patients who return home in independent isolation at home or who were referred. This consequences in a non-differential misclassification of the symptom severity variable, but if there was, it would result in underestimated associations. Third, ideally, the reference date for determining vaccination status was the date of disease onset or the date of PCR test, but in this study, we used the date of hospital admission as a reference due to limited data. Even though we

controlled for other variables such as age, gender, and comorbid status in the multivariate analysis, the association values obtained might still be confused by other confounder variables that could not be assessed in this study, such as a history of previous COVID-19 infection.

Conclusion

Amid the circulation of the Omicron variant, the COVID-19 vaccine has been shown to reduce the risk of severe COVID-19 disease with a higher level of protection in the third dose of vaccination. The results of this study also showed that the elderly group (> 60 years), group with comorbidities, and the male gender had lower vaccine effectiveness and were at higher risk of experiencing the severity of COVID-19. For this reason, accelerated efforts from the government and public awareness were needed to increase the coverage of booster doses of vaccination. In addition, special attention or priority was needed for the elderly group, groups with comorbidities, and men in the COVID-19 countermeasures program, such as booster vaccinations, case detection, and management to prevent the severity and mortality. Further prospective studies were needed to monitor the effectiveness and duration of vaccine protection as other new variants of the SARS-CoV-2 virus emerge.

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Conflict of Interest

The author declares that there is no conflict of interest in writing this article.

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