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Vaccination with the Incidence of Post-Acute Sequelae COVID-19

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Abstract

Post-acute sequelae COVID-19 (PASC) symptoms are present in the vast majority of COVID-19 survivors, even those who have received the COVID-19 vaccine. Until now, vaccines against PASC are still controversial. Some previous findings suggest that vaccines can reduce or worsen PASC symptoms. In addition, there has been no related research in North Maluku Province, especially in Ternate City. This study aims to determine the relationship between vaccine administration and PASC based on the total dose and type of vaccine obtained using a questionnaire-based cross-sectional design questionnaire. The study population was COVID-19 patients diagnosed with RT-PCR or RDT-Ag in 2020–2022, domiciled in Ternate City. The respondents were 133 people. Bivariate analysis showed no effect of vaccine dose administration on the incidence of PASC (P=0.111). Similarly, the type and dose of vaccine based on the did not affect (first dose, P = 1.000), (second dose P = 0.732), and (booster P = 0.434) PASC. In terms of the timing of booster doses, pre- and post-COVID-19, there was no significant effect (P=0.384). However, there was a higher incidence of PASC in responders who received the booster dose post-COVID-19. There is no association between vaccine administration and the incidence of PASC.

Introduction

The respiratory illness called Coronavirus Disease 2019 (COVID-19) is caused by the SARS-CoV-2 coronavirus. COVID-19 has created an extremely hazardous and lethal threat to public health around the world, including in Indonesia (Madabhavi *et al*., 2020; Shi *et al*., 2020). According to the Republic of Indonesia's Ministry of Health, as of September 24, 2022, 6.4 million positive cases have been confirmed, and 158 thousand COVID-19 deaths have been reported in Indonesia (Infeksi Emerging, 2022). Positive cases of COVID-19 in Ternate City as of September 21, 2022, were 3.4 thousand, and 88 of them died (Dinas Kesehatan Kota Ternate, 2022). Most SARS-CoV-2 virus-infected individuals recover within 14 days (Madabhavi *et al*., 2020). This is in line with research conducted at Dr. H. Chasan Boesoirie Ternate Hospital showing that most patients infected with COVID-19 recovered after treatment (Masrika *et al*., 2022). However, several studies have shown that the majority of individuals can still experience symptoms weeks or even months after the COVID-19 acute phase has passed. This disease is referred to as "post-acute sequelae COVID-19" (PASC) (Lerner *et al*., 2021; Logue *et al*., 2021).

PASC is most commonly reported in Asia with a prevalence of 49%, while the lowest prevalence in North America is 30% (Chen *et al*., 2021). Meanwhile, the prevalence of PASC in Indonesia was reported as 66.5% (Susanto *et al*., 2022). Symptoms of PASC that arise can affect several systems in the human body, for example, cardiovascular, respiratory, musculoskeletal, and neurological (Hayes *et al*., 2021). A meta-analysis showed that 80% of COVID-19 survivors experienced at least one PASC symptom, the most common being

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fatigue, headache, impaired concentration, hair loss, and shortness of breath (Leon *et al*., 2021). Ninety percent of PASC patients had continuing symptoms nine months after the COVID-19 acute phase, and 67% had not resumed their prior levels of activity (Davis *et al*., 2021; Tran *et al*., 2022).

An influential way of struggling against COVID-19 is developing a vaccine (Zheng *et al*., 2022). More than 12.4 billion doses of the COVID-19 vaccine have been administered globally as of August 2022 (*COVID-19 Dashboard*, 2022). Meanwhile, in September 2022, COVID-19 vaccine coverage in Indonesia reached 437 million doses, with 246 thousand doses including vaccine administration in Ternate City (Global Situation Report, 2022). It has been shown that receiving a COVID-19 vaccine lowers the risk of contracting a serious illness and passing away from COVID-19 (Zheng *et al*., 2022). Given that the COVID-19 vaccination only partially prevents the spread of the SARS-CoV-2 virus, it is possible for people who have received it to acquire PASC (Wang *et al*., 2022). In actuality, PASC can have an impact on a variety of patients, from those who are asymptomatic to those who experience severe symptoms during an acute COVID-19 infection and require critical care (Sudre *et al*., 2021; Tenforde *et al*., 2020). It is still unclear how vaccination affects a wide range of PASC.

In the literature, the vaccination effect on PASC is controversial. Findings from one study showed that vaccination reduced some symptoms 6 months after infection, but not all symptoms of PASC (Antonelli *et al*., 2022). According to American studies, even if a patient just receives one dose of the vaccination, they are less likely to acquire PASC than those who receive the vaccine after contracting COVID-19 (Simon *et al*., 2021). However, another study reported that 20% of individuals infected after the vaccine experienced PASC for more than 6 weeks (Hoque *et al*., 2021). Furthermore, there is a lack of studies to explore the impact of booster vaccines on PASC. Studies that identified differences in response between vaccine types showed that the Pfizer vaccine was more effective than the Janssen vaccine in reducing the risk of PASC (Notarte *et al*., 2022). Based on the above problems, research on the association of vaccine administration with the incidence of PASC needs to be carried out, considering that this is still a question because the results of previous studies are still controversial and there has been no related research in North Maluku Province, especially Ternate City.

Method

The research being conducted was quantitative and employed a cross-sectional technique with an analytical observational design. The research was located in the city of Ternate and conducted for two weeks in February 2023. The study's population consists of patients who had a COVID-19 diagnosis by RT-PCR or RDT-Ag in 2020–2022, and who were either born in or had lived in Ternate City. A population that satisfies the inclusion and exclusion criteria constitutes the sample for this investigation. Being diagnosed with COVID-19 by RT-PCR or RDT-Ag, receiving at least one dose of COVID-19 vaccination, being younger than 18 years old, agreeing to participate in the trial by signing an informed consent form, and being able to read and speak coherently were the inclusion criteria for the study. The exclusion category in this study was that the questionnaire was not filled in completely and the respondent was diagnosed with COVID-19 <4 weeks before filling out the questionnaire. Demographic factors, vaccination status (including time, doses, and time to administer vaccine) as well as comorbidities were collected from the participants using the questionnaire. The PASC is defined as any self-reported residual symptoms linked to COVID-19.

The sample size was estimated from a different proportion of patients having any residual symptoms that belong to PASC between fully vaccinated and non-fully vaccinated from one study in Indonesia (Herman, Wong, *et al*., 2022). Assuming 5% type 1 error and the proportion of fully-vaccinated people who experienced PASC was 18.5% and unvaccinated people with PASC was 34.6%, power study 99% with one tail hypothesis and dropout response of 15%, the number of research subjects needed was 133 respondents, taken using the purposive sampling technique. Research subjects were taken by visiting patients' homes. The data

that has been obtained is processed using the SPSS 26.0 program with univariate and bivariate methods. Bivariate processing used chi-square analysis and Fisher's exact test. The implementation of this research has received approval from the Ternate City National and Political Unity Agency with number 070/864/BKBP/2022 and the University of Sebelas Maret Faculty of Medicine Research Ethics Commission with number 28/UN27.06.11/KEP/EC/2023.

Result and Discussion

This study is a type of observational analytic study that was conducted in Ternate City in February 2023 with 133 respondents who met the inclusion and exclusion criteria. The research findings are shown in the table below based on the data collected and analyzed:

Table 1. Distribution of Respondents Based on Incidence

Distribution of respondents based on the incidence of PASC	Frequency	Percentage
PASC	91	68,4
Non PASC	42	31,6
Total	133	100%

Based on Table 1, the research subjects who experienced PASC were 91 (68.4%) people, and the research subjects who did not experience PASC were 42 (31.6%) people. These results are in line with research conducted in Indonesia, which stated that 66.5% of COVID-19 patients experienced PASC (Susanto *et al.*, 2022). Meanwhile, PASC is most commonly reported in Asia, with a prevalence of 49% (Chen *et al.*, 2021).

Table 2. Distribution of Respondent Characteristics

Respondent characteristics	PASC (n=91)		Non-PASC (n=42)		Total	P value
	F	%	F	%		
Age (years old)						
18-25	59	71,1%	24	28,9%	83	
26-35	17	70,8%	7	29,2%	24	
36-45	10	55,6%	8	44,4%	18	0,605*
46-55	5	62,5%	3	37,5%	8	
56-65	0	0%	0	0%	0	
>65	0	0%	0	0%	0	
Gender						
Female	60	71,4%	24	28,6%	84	0,433*
Male	31	63,3%	18	36,7%	49	
Comorbid disease						
None	85	69,1%	38	30,9%	123	
Mental disorders	0	0%	0	0%	0	
Diabetes mellitus	0	0%	0	0%	0	
Hypertension	3	50%	3	50%	6	
Heart disease	0	0%	1	100%	1	
Kidney disease	1	100%	0	0%	1	0,570**
Autoimmune disease	0	0%	0	0%	0	
Tuberculosis	1	100%	0	0%	1	
COPD	0	0%	0	0%	0	
Cancer	0	0%	0	0%	0	
HIV/AIDS	0	0%	0	0%	0	
Asthma	1	100%	0	0%	1	
Total Vaccine Dose						
Dose 1	5	55,6%	4	44,4%	9	0,111*
Dose 2	14	53,8%	12	46,2%	26	
Dose booster	72	73,5%	26	26,5%	98	

Respondent characteristics	PASC (n=91)		Non-PASC (n=42)		Total	P value
	F	%	F	%		
Type of first dose vaccine						
In-active	3	60%	2	40%	5	1.000**
Adenovirus vectors	0	0%	0	0%	0	
m-RNA	2	50%	2	50%	4	
Type of second dose vaccine						
In-active	11	50%	11	50%	22	0.732**
Adenovirus vectors	1	50%	1	50%	2	
m-RNA	2	100%	0	0%	2	
Type of booster dose vaccine						
In-active	7	53,8%	6	46,2%	13	0,434*
Adenovirus vectors	14	73,7%	5	26,3%	19	
m-RNA	39	59,1%	27	40,9%	66	

Abbreviations: *, chi square; **, fisher exact text

Based on Table 2, the age group of 18-25 years experienced the most PASC. The analysis between age and PASC incidence showed non-significant results, which indicates that there is no significant association between age and PASC incidence. This finding is consistent with a New York prospective cohort study that showed no association between age and symptoms after COVID-19 (Wisnivesky et al., 2022). The study data showed that females experienced more PASC than males. The analysis of gender and the incidence of PASC yielded non-significant results. This demonstrates that there is no apparent association between gender and the prevalence of PASC. This finding is in line with research in New York showing that there is no relationship between gender and symptoms after COVID-19 (Wisnivesky et al., 2022). In opposition, the findings of a study conducted at Milan's San Paolo Hospital suggest that women are three times more likely to develop PASC than men (Bai et al., 2022). This is thought to be related to the hormone estrogen, which can prolong the acute inflammatory phase even after recovery. In addition, it has been reported that women produce strong IgG antibodies early in the disease phase. This may result in a more favorable outcome, but may also prolong earlier disease manifestations (Bai et al., 2022; Rudroff et al., 2022).

Based on Table 2, the most common comorbid diseases owned by patients with PASC are kidney disease, tuberculosis, and asthma. The results of the analysis of comorbid diseases with the incidence of PASC showed p=0.729 (p>0.05). This means there is no meaningful association between comorbidities and the incidence of PASC. The findings of a retrospective study showed that comorbid diseases are one of the risk factors for PASC (Abdelwahab *et al*., 2022). Different results were found because most of the respondents in this research were in the late adolescent age group. Therefore, the majority of PASC patients did not have comorbidities.

According to the results of Table 2, the total vaccine dose received by respondents was not significantly associated with the incidence of PASC. This finding was not linear with a local study showing that 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) (Masrika *et al*., 2023) However a cohort study done in Norway, demonstrated no appreciable difference in PASC presentation between those who had the vaccine and those who hadn't after 3 to 15 months of acute COVID-19 infection (Brunvoll *et al*., 2022). According to the prospective Amsterdam cohort study, there isn't any conclusive proof that vaccination reduces the symptoms of PASC. This is supported by serological data demonstrating no difference between responders with and without PASC in baseline neutralizing antibody titers at three months after disease onset or in antibody decay at nine months after disease onset (Wynberg *et al*., 2022). In addition, no research has been conducted to investigate the impact of booster vaccines on PASC (Notarte *et al*., 2022).

Based on the vaccination's mechanism of action in the first, second, and booster doses, there is no statistically significant link between the incidence of PASC and the vaccine types given in Table 2. The observational cohort analysis revealed that, regardless of the vaccine type, there is little statistical support for a connection between immunization and PASC symptoms. These findings concur with observational studies conducted in the UK, which found that giving PASC patients the COVID-19 vaccine via mRNA or adenoviral vectors did not enhance their symptoms or quality of life (Arnold *et al*., 2021). The uneven distribution of respondents' vaccine types may reduce the generalizability of the findings. One problem in recruiting respondents with different vaccine types is vaccine procurement in Indonesia, where some vaccines with different mechanisms of action were not widely available to the public during the recruitment period. In addition, the decline in cases in Indonesia hampered recruitment with different vaccines (Herman, Viwattanakulvanid, *et al*., 2022).

The symptoms that a significant number of respondents reported following an acute episode of COVID-19 were fatigue (57.2%), anosmia (52.8%), cough (50.5%), sore throat (45.1%), and fever (39.6%), according to the study findings in Table 3. Similar findings in India indicated that the most frequently reported symptoms were fever (64.9%), cough (45.4%), headache (18.3%), difficulty breathing (16%), olfactory dysfunction (12.9%), and taste dysfunction (12.3%) (Arjun *et al*., 2022). Moreover, most neurological and psychiatric symptoms did not persist for more than 4 weeks, contrary to a previous study showing the presence of neuropsychiatric symptoms more than four weeks after COVID-19 (Herman, Bruni, *et al*., 2022). There is strong evidence that many viral infections resolve months or even years after recovery from COVID-19 tiredness that develops a few weeks after an acute sickness. SARS-CoV, West Nile, Ebola,

Table 3. Distribution of Clinical Symptoms of PASC Based on Duration Experienced

Criteria	No Symptoms	Lasts up to 4 weeks from symptom onset or diagnosis	Persist >4-8 weeks from symptom onset or diagnosis	Persist >8-12 weeks from symptom onset or diagnosis	Persist >12 weeks from symptom onset or diagnosis	Total
Fatigue	39 (42,9%)	44 (48,4%)	3 (3,3%)	1 (1,1%)	4 (4,4%)	91
Fever	55 (60,4%)	33 (36,3%)	1 (1,1%)	0 (0%)	2 (2,2%)	91
Headache	57 (62,6%)	30 (33%)	0 (0%)	1 (1,1%)	3 (3,3%)	91
Vertigo	81 (89%)	10 (11%)	0 (0%)	0 (0%)	0 (0%)	91
Cough	45 (49,5%)	38 (41,8%)	6 (6,6%)	0 (0%)	2 (2,2%)	91
Sore throat	50 (54,9%)	38 (41,8%)	2 (2,2%)	0 (0%)	1 (1,1%)	91
Hoarseness	72 (79,1%)	18 (19,8%)	1 (1,1%)	0 (0%)	0 (0%)	91
Dyspnea	74 (81,3%)	15 (16,5%)	1 (1,1%)	0 (0%)	1 (1,1%)	91
Anosmia	43 (47,3%)	41 (45,1%)	3 (3,3%)	1 (1,1%)	3 (3,3%)	91
Runny nose	59 (64,8%)	28 (30,8%)	1 (1,1%)	0 (0%)	3 (3,3%)	91
Chest pain	81 (89%)	9 (9,9%)	1 (1,1%)	0 (0%)	0 (0%)	91
Muscle pain	57 (62,6%)	32 (35,2%)	1 (1,1%)	0 (0%)	1 (1,1%)	91
Abdominal pain	83 (91,2%)	8 (8,8%)	0 (0%)	0 (0%)	0 (0%)	91
Diarrhea	85 (93,4%)	5 (5,5%)	1 (1,1%)	0 (0%)	0 (0%)	91
Loss of consciousness	90 (98,9%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	91
Concentration disorder	77 (84,6%)	12 (13,2%)	1 (1,1%)	0 (0%)	1 (1,1%)	91
Depression	84 (92,3%)	7 (7,7%)	0 (0%)	0 (0%)	0 (0%)	91
Anxiety	75 (82,4%)	15 (16,5%)	0 (0%)	0 (0%)	1 (1,1%)	91
Others	84 (92,3%)	2 (2,2%)	1 (1,1%)	0 (0%)	4 (4,4%)	91

and influenza A (H1N1) virus outbreaks have all been linked to chronic fatigue in the past, particularly in people under the age of 30. This may be due to miscommunication in the pathways of inflammatory response, especially tissue cytokines (Shukla and Misra, 2022). The olfactory bulbus is very important in eliminating pathogens invading prone entry sites early and quickly. According to Imam *et al.* (2020), the post-viral olfactory impairment linked to COVID-19 is comparable to that linked to other viral infections such as metapneumovirus, parainfluenza, influenza, and rhinovirus (Imam *et al.*, 2020).

Table 4. The Relationship between the Timing of Vaccine Administration and the Incidence of Post Acute Sequelae of COVID-19

PASC occurrence	Time of vaccine administration#		Total	Significance
	Pre-COVID-19	Post-COVID-19		
PASC	15 (20,8%)	57 (79,2%)	72 (100%)	0,384**
Non-PASC	3 (11.5%)	23 (88.5%)	26 (100%)	
Total	18 (18,4%)	80 (81,6%)	98 (100%)	

Abbreviations: #, doses booster; **, fisher exact test.

The results in Table 4 show that respondents who received boosters after COVID-19 experienced more PASC compared to respondents who received a booster vaccine before COVID-19. The time of administration of the booster vaccine had no significant association with the incidence of PASC. This study supports the findings of a literature analysis showing those who have received a vaccination before having a lower risk of developing PASC. This is based on two hypotheses. First, vaccinations might diminish the severity of an acute COVID-19 infection, reduce the chance of developing systemic illnesses, or hasten the development and duration of PASC symptoms. The second hypothesis is that the vaccine accelerates the elimination of residual SARS-CoV-2 virus in humans or reduces excessive inflammatory and/or immune responses related to PASC symptoms (Notarte *et al.*, 2022). A Japanese study showed that individuals who experienced worsening PASC symptoms after vaccination were individuals who experienced an increase in antibody titer rates, resulting in an excessive immune response to vaccination (Tsuchida *et al.*, 2022).

A study in France suggested that vaccination after COVID-19 infection reduced symptom severity at 120 days (Tran *et al.*, 2021). Other findings in Switzerland showed that the vaccine was associated with a reduced prevalence of PASC symptoms (Tran *et al.*, 2021). Other findings in Switzerland suggest that vaccination is associated with a reduced prevalence of PASC symptoms (Nehme *et al.*, 2022). The hypothesis is the possible amelioration of immune or inflammation response dysregulation, or the possible removal of surviving viruses or SARS-CoV-2 viral remnants (Nehme *et al.*, 2022). The disparity in these results is probably caused by the fact that COVID-19 infection can result in the production of a large number of autoantibodies and that the effectiveness of COVID-19 vaccinations depends on the host's immunological response. By destroying the viral reservoir and resetting the immune system's response to the initial acute infection, the COVID-19 vaccine reduces PASC. The effect may vary depending on the host (Notarte *et al.*, 2022).

Conclusion

Based on the results of the study, the researchers concluded that there was no significant link between vaccination and the occurrence of post-acute sequelae of COVID-19. However, a higher incidence of PASC was found in respondents who received a total dose of the vaccine up to a booster dose, the adenovirus vector vaccine type, and obtained the booster vaccine after being infected with COVID-19.

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