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Vaccination Status and Symptom Severity in Covid-19 Patients

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Abstract
We are still attempting to reduce COVID-19 morbidity and mortality through several means, including immunization. In early December 2021, Indonesia had 49.19% coverage of the second COVID-19 vaccination. Researching and collecting data on the association between vaccine completion and symptom severity is critical to persuade individuals to vaccinate. This study aims to examine the relationship between COVID-19 vaccination status and the degree of symptom severity in COVID-19 patients. This cross-sectional study used secondary data from the medical records of COVID-19 patients at the PDHI Yogyakarta Islamic Hospital from June to October 2021. The "PeduliLindungi" application was used to acquire vaccination status information. We used the chi-square test and multiple logistic regression for bivariate and multivariate analyses. The study enrolled 112 participants who met the criteria. The severity of COVID-19 symptoms was related to vaccination status and hypertension. Patients who were unvaccinated or had only partially vaccinated were 62.383 times more likely to develop severe and critical severity (aOR 62.383; 95% CI 12.129-320.861). Patients with hypertension were 3.643 times more likely than those without hypertension to experience severe or critical symptoms (aOR=3.643; 95% CI 1.025-12.952). Male gender, elderly age, chronic lung illness, and diabetes mellitus slightly increased the likelihood of severe symptoms but were not statistically significant. Complete immunization is strongly advised to reduce the risk of severe or critical symptoms.

Keywords: COVID-19, Severity of Symptom, Vaccination Status.

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1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) is a highly contagious disease that mostly affects the human respiratory tract. The disease is caused by the Coronavirus Severe Acute Respiratory Syndrome 2 (SARS-CoV-2). In late December 2019, physicians in Wuhan, Hubei, China, discovered many patients with pneumonia-like clinical symptoms of unclear cause (Huang et al., 2020). Then, in early January 2020, the first case of death of a 61-year-old man was reported due to infection with the new coronavirus, which was later named SARS-CoV-2 (Keni et al., 2020). The virus then spread rapidly across many countries and continents, prompting the World Health Organization (WHO) to declare it a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and then to a pandemic on March 11, 2020 (Özdemir, 2020; Wang et al., 2020; World Health Organization, 2020).

The COVID-19 pandemic entered its second wave in mid-2021, from June to October (SATGAS COVID-19, 2021). The second wave peaked in July 2021, with up to 50,000 new cases each day. Every day, the Special Region of Yogyakarta contributed around 1,000 new cases (Winduajie, 2021). As of July 13, 2021, the bed occupancy rate (BOR) in COVID-19 referral hospitals in Yogyakarta Special Region Province was 98.42% (CNN Indonesia, 2021). The high COVID-19 BOR from June to October 2021 was caused by SARS-CoV-2 delta mutant infection, which resulted in more severe symptoms (Lauring et al., 2022).

The efforts made by the government in controlling COVID-19 in the health sector consist of 3 things, namely, 3M, consist of "Memakai masker, Mencuci tangan dengan sabun, and Menjaga Jarak/ Menghindari Kerumunan (wearing a mask, physical distancing, avoiding crowds, and washing hands with soap), 3T (testing, tracing, and treatment), and vaccination. Vaccination is an action that aims to raise a person's immunity by providing antigenic substances that are expected to protect a person from being infected with microorganisms or prevent severe symptoms when infected. Several vaccine modalities are developed to generate immunity against SARS-CoV-2: inactivated virus, viral vector, nucleic acid, and protein sub-units. The various vaccine modalities will form an adaptive immune system, namely CD4+ and CD8+ T cells and IgG and IgA antibodies. These antibodies neutralize the virus by preventing the binding of the virus to its receptors found in the host cell or inhibiting the conformational changes required by the virus to fuse with the cell membrane (Speiser & Bachmann, 2020).

Despite many vaccination promotion campaigns, public resistance to vaccination remained high in early to mid-2021. Coverage is decreasing since Indonesia continues to rely on imported vaccinations. Many health staff, as well as regular people, continue to resist the COVID-19 vaccine. In 2021, healthcare workers' acceptance of the COVID-19 vaccine remains less than 75% (Sallam, 2021). Some reasons for vaccination rejection include safety concerns, misinformation or a lack of knowledge, adverse effects and efficacy, and a lack of trust in professionals, the government, or medicine manufacturers (Arce et al., 2021; Sallam, 2021). Another cause for rejection is religious considerations, particularly the halal status of vaccination goods (Nugraheni & Sulistyawati, 2023).

The total national COVID-19 vaccination achievements for doses one and two as of December 11, 2021, are 145,910,019 (70.06%) and 102,445,257 (49.19%), respectively. Vaccination coverage and the public's enthusiasm to get vaccines vary by region (Indonesian Ministry of Health, 2021). WHO and the government of the Republic of Indonesia are working to increase vaccination coverage. Studies on the effectiveness and benefits of already available vaccines continue to be conducted. Information about the usefulness of vaccines to prevent and reduce the severity of symptoms of people exposed to COVID-19 is crucial and affects the interest of citizens in vaccinating. This study was conducted to determine the relationship between previous vaccination and the severity of symptoms in patients diagnosed with COVID-19 who were hospitalized.

2. RESEARCH METHOD

This *cross-sectional* research was conducted at the PDHI Yogyakarta Islamic Hospital and lasted about eight months, from preparing the research proposal to preparing the research report. Data collection was conducted in September-October 2022. Patients diagnosed with COVID-19 and hospitalized at the PDHI Yogyakarta Islamic Hospital between June and October 2021, aged 26 to 80, were eligible for this study. This June-October 2021 is the peak period of the number of COVID-19 patients undergoing hospitalization at the PDHI Yogyakarta Islamic Hospital.

We excluded the patients with incomplete medical record data from this study. Two hundred fifty-eight patients diagnosed with COVID-19 were hospitalized at the PDHI Yogyakarta Islamic Hospital from June to October 2021. Only 116 patients have a known history of the date and year of getting the vaccine. The vaccination status of the patients included first-dose *booster vaccine* for health workers, second-dose vaccine, first-dose vaccine, and unvaccinated. Furthermore, 4 out of 116 patients were excluded from the study due to incomplete medical record data. Patients with COVID-19 severity not recorded in medical records, patients referred to other health institutions, or patients who died before the severity was established were all excluded from this study. In the end, only 112 patients participated in this study, consisting of 56 patients with complete Vaccination status and 56 patients with Incomplete Vaccination status (Figure 1).
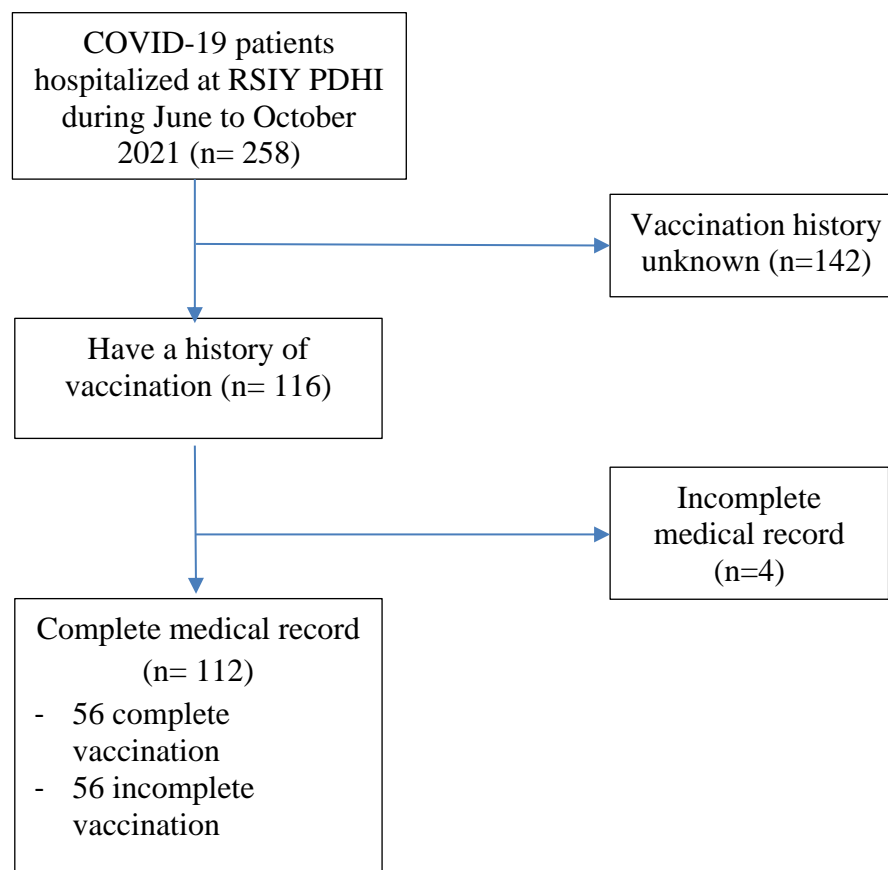
Figure 1. Flow of the selection of the research subjects

This study uses secondary data from patient medical records. Data taken from the medical record includes age, gender, COVID-19 test results based on antigen swab or PCR, severity of symptoms, comorbid history of patients such as chronic lung disease, diabetes mellitus, and

hypertension, smoking, therapy given to patients in the form of antiviral, vitamin, and oxygenation.

The independent variable in this study is COVID-19 vaccination status, while the dependent variable is the severity of COVID-19 symptoms. Vaccination status is the medical record obtained from the patient or family information and proof of vaccination certificate from the Pedulilindungi app. Complete Vaccination is a group of patients who have received at least two vaccine doses. At the same time, incomplete Vaccination is a group of patients who have not received a vaccine or have only received the first dose. The grade of the patient's severity is determined by the attending physician and documented in the medical record. External variables include age, gender, smoking, chronic lung disease, hypertension, and diabetes mellitus. Bivariate analysis was performed using chi-square and binomial regression. Odds Ratio was used to express associations, with a p-value <0.05. Binomial logistic regression was applied in multivariate analysis, with adjusted odds ratios and p-values <0.05 indicating significance.

This study has obtained a certificate of ethical review from the Ethics Committee of the Islamic University of Indonesia with Letter No. 6/Ka.Kom.Et/70/KE/IX/2022 and approval from the Ethics Committee and Medical Records Installation of the PDHI Yogyakarta Islamic Hospital.

3.   RESULTS AND DISCUSSION

The factors evaluated were described using univariate analysis. The independent variables included vaccination status, age category, gender, smoking habit, history of chronic lung disease, hypertension, and diabetes mellitus, while the dependent variable was the severity of symptoms. The frequency distribution of these variables is presented in Table 1.

Table 1. Characteristics of Inpatients Diagnosed with COVID-19 at Yogyakarta PDHI Islamic Hospital (n=112)

Characteristics	Frequency	Percentage (%)
Vaccination Status		
Incomplete	56	50.0
Complete	56	50.0
Age category		
Old and elderly	53	47.3
Young and middle	59	52.7
Gender		
Male	57	50.9
women	55	49.1
Smoking		
Yes	38	33.9
no	74	66.1
Chronic lung disease		
Yes	7	6.3
No	105	93.7
Hypertension		
Yes	47	42.0
No	65	58.0
Diabetes mellitus		
Yes	42	37.5
No	70	62.5

Table 1 shows that the mean age of the patients was 58.41 years, with the youngest being 27 years and the oldest being 80 years. The majority of the patients were men (50.9%), nonsmokers (66.1%), did not smoke, did not have chronic lung disease (93.7%), had normal blood pressure (58%), and did not have diabetes mellitus (62.5%). Bivariate analysis determined the relationship between the independent and dependent variables. The analysis results are statistically significant when a *p-value* <0.05 is obtained. Table 2 displays the findings of the bivariate analysis. According to the findings, old age, smoking, and insufficient immunization, all enhance the likelihood of a person exposed to COVID-19 suffering severe or critical symptoms.

Table 2. Relationship between patient characteristics and symptom severity (n=112)

Variable	Degree of Severity		p-value	OR (95% CI)
	Severe or Critical	Mild or Moderate		
Gender				
Male	36	21	0.589	1.3 (0.62-1.83)
women	31	24		
Age				
Old/elderly	38	15	**0.025***	2.6 (1.19-5.75)
Young adults	29	30		
Smoking				
Yes	30	8	**0.006***	3.75 (1.520-9.254)
No	37	37		
Vaccination				
Incomplete	52	4	**0.000***	35.5 (10.96-115.23)
Complete	15	41		
Chronic Lung Disease				
Yes	4	3	1.000	0.889 (0.189-4.176)
No	63	42		
Hypertension				
Yes	24	3	0.158	0.534 (0.247-1.152)
No	43	42		
Diabetes mellitus				
Yes	22	20	0.296	0.611 (0.281-1.331)
No	45	25		

OR= Odds Ratio
CI= Confidence Interval
*p-value <0.05

Table 2 is multivariate analysis was conducted to determine the association of several independent variables with the degree of severity of COVID-19. The analysis showed that incomplete vaccination and hypertension significantly increased the risk of a person exposed to COVID-19 experiencing severe or critical symptoms. A person with incomplete vaccination had a 62.383 times higher risk of severe or critical symptoms than those with complete vaccination (p-value 0.000, 95% CI 12.129-320.861). Those with hypertension had a 3.643 times higher risk of severe or critical symptoms than those without (p-value 0.046, 95% CI 1.025-12.952). Meanwhile, male gender, old age, chronic lung, and DM slightly increased the risk of someone exposed to the COVID-19 virus having severe or critical symptoms, but not statistically significant.

Table 3. Results of Multiple Logistic Regression Analysis (n=112)

Variable	Degree of Severity		p-value	aOR (95% CI)
	Severe or Critical	Mild or Moderate		
Gender				
Male	36	21	0.386	1.905
women	31	24		(0.444-8.177)
Age				
Old/elderly	38	15	0.556	1.547
Young adults	29	30		(0.362-6.614)
Smoking				
Yes	30	8	0.505	0.553
No	37	37		(0.097-3.159)
Vaccination				
Incomplete	52	4	**0.000***	**62.383**
Complete	15	41		**(12.129-320.861**
Chronic Lung Disease				
Yes	4	3	0.999	1.002
No	63	42		(0.088-11.453)
Hypertension				
Yes	24	3	**0.046***	**3.643**
No	43	42		**(1.025-12.952)**
Diabetes mellitus				
Yes	22	20	0.261	1.925
No	45	25		(0.615-6.021)

aOR= adjusted Odds Ratio
CI= Confidence Interval
*p-value<0.05

Table 3 shows that sixty-seven of 112 subjects (59.8%) had severe or critical severity. From June to October 2021, the second wave of COVID-19 occurred in Indonesia. Not all patients could access hospitals during this period (SATGAS COVID-19, 2021). The peak of the second wave occurred in July 2021, with up to 50,000 new cases every day. The Special Province of Yogyakarta contributed more than 1,000 new cases every day. Hospitals are prioritized for patients with severe or critical symptoms, while patients with asymptomatic, mild, or moderate symptoms are advised to self-isolate or be treated in shelters. July 13, 2021, the *bed occupancy rate (BOR)* in COVID-19 referral hospitals in Yogyakarta Special Region Province reached 98.42% (Damarjati, 2021). The high BOR due to COVID-19 from June to October 2021 was caused by SARS-CoV-2 delta variant infection, which causes more severe symptoms (Wang et al., 2020).

The results of multivariate analysis showed that the severity of symptoms in COVID-19 patients was significantly associated with vaccination and hypertension. Male gender, old age, chronic lung disease, and DM also increased the risk of a person exposed to COVID-19 having severe or critical symptoms, but not significantly.

People who have not received a complete Covid-19 vaccine, have not been vaccinated, or have only received one dose have a 62 times higher risk of experiencing severe or critical symptoms if exposed to Covid-19 than those who have received a complete vaccine. Various existing vaccine modalities will trigger the formation of antibodies and $CD4^+$ and $CD8^+$ T cells. Ig G and Ig A will neutralize the virus by inhibiting the binding of SARS-CoV-2 to its receptor found on ACE2 or preventing the conformational changes required for the virus to fuse with the cell membrane (Speiser & Bachmann, 2020). IgA plays a role in preventing infection in airway mucosa, epithelial cells, and endothelial cells. $CD4^+$ and $CD8^+$ T cells will recognize

viral antigens (Sridhar et al., 2013). The protective effect provided by this vaccine started to occur in the first 14 days after getting the first vaccination dose (Bhattacharya et al., 2021). However, the effect will decrease up to 4 times after ten weeks of the second vaccination dose (Agrawal et al., 2020). Booster vaccination will provide a more significant protective effect in preventing the severity of COVID-19 (Ng et al., 2022).

COVID-19 severity is classified into five stages based on the appearance of signs and symptoms: asymptomatic, mild, moderate, severe, and critical. Patients who have been confirmed positive for SARS-CoV-2 infection but are asymptomatic are classified as asymptomatic. Patients with moderate symptoms have a fever of 38^0C that improves without therapy with or without coughing, no dyspnea, indicators of shortness of breath or chronic disease, and no signs of pneumonia on thoracic X-ray examination (Baj et al., 2020; Zu et al., 2020). Patients with moderate severity generally have a persistent fever with dry cough, pneumonia-like symptoms, and signs of pneumonia from thoracic auscultation, physical examination, and thoracic X-ray examination. Severe symptoms when one of the following criteria is met: oxygen saturation <90% on room air, respiration rate >30 times/minute in adults, and signs of severe respiratory distress characterized by the use of additional muscles when breathing and the inability to complete speech in one complete sentence. Patients are critical if they have any criteria: ARDS *(Acute Respiratory Distress Syndrome),* sepsis, septic shock, extrapulmonary organ dysfunction, or other conditions requiring life support therapy such as mechanical ventilation. Patients who satisfy any of the following characteristics are critical: Acute Respiratory Distress Syndrome (ARDS), septicemia, septic shock, extrapulmonary organ failure, or other illnesses needing life-sustaining care such as mechanical ventilation (World Health Organization, 2020).

Based on bivariate analysis using the chi-square test, a p-value of 0.158 was obtained, which statistically means no significant relationship exists between hypertension and severity. However, the results of multivariate analysis using multiple logistic regression obtained a p-value of 0.025, which statistically explains that hypertension is one of the most vital risk factors associated with symptom severity. According to Freund et al. (2022), vaccination is the main protective factor from risk factors for the severity of COVID-19 patients who have hypertension (Freund et al., 2022). This means that hypertension is not an independent factor that affects the severity of Covid-19 in patients.

Old age and elderly patients were 2.6 times more at risk of severe and critical severity, although not statistically significant. Old age is associated with typical immune system aging characterized by decreased levels of CD4$^+$ and CD8$^+$ T lymphocytes, whereas typically, lymphocytes will increase in response to viral infections (Liu et al., 2020). According to Tizazu, Mengist, and Demeke (2022), there are also immunological and physiological changes in the airway in old age. Immunological changes in old age are characterized by increased proinflammatory cytokines such as IL-6, *CRP (C-reactive protein),* TNF-α, IL-18, and IL-β. These high levels of proinflammatory cytokines cause the immune system response to SARS-CoV-2 to become hyperactive. It will trigger a *cytokine storm,* resulting in severe tissue damage, ARDS, and multiorgan failure. Changes in the airway's physiology might impair the system for eliminating foreign materials from the airway by diminished muscular strength and cilia malfunction. In addition, the amount of proinflammatory cytokines mentioned above will be much higher in elderly patients with comorbidities such as DM or chronic kidney disease (Tizazu et al., 2022).

Male patients were more at risk of experiencing more severe symptoms than female patients, although it was not statistically significant. The findings of this study contrast those of Stalter et al. (2022), who discovered a statistically significant association between sex and severity with a p-value of 0.001 (Stalter et al., 2022). According to Vahidy et al. (2021) and Stalter et al. (2022) research, men are more likely to experience more severe and critical

symptoms as a result of comorbidities such as heart disease, high blood pressure, diabetes mellitus, and chronic pulmonary disease (Stalter et al., 2022; Vahidy et al., 2021).

The bivariate analysis with *chi-square* showed a significant relationship between smoking and the symptom severity of COVID-19 patients (p-value=0.006), but the multivariate analysis showed no relationship. Smoking patients experience increased infiltration of inflammatory cells in the mucosal tissue, submucosa, and airway glands. It will induce increased mucus production and epithelial cell hyperplasia, disrupt tissue repair, thicken the airway wall, and disrupt lung function, including gas exchange function and decreased foreign body clearance from the airway (He et al., 2022). Smoking will also cause increased expression of angiotensin-converting enzyme 2 (ACE2) in type II pneumocytes, myocardium, and gastrointestinal tract cells and inhibit interferon activity, which is vital in stimulating infected cells to produce proteins to attack the virus (Wu et al., 2020).

The multivariate analysis show that the history of chronic lung disease slightly increases the risk of COVID-19 patients experiencing severe symptoms, although this is not statistically significant. This study's results differ from the research conducted by Wu et al. (2020). During the early and peak COVID-19 pandemic, individuals with chronic lung disease were more cautious and implemented stricter infection transmission prevention measures (Wu et al., 2020). Social restriction policies also reduce contact with others and simultaneously reduce the risk of exposure. Transportation mobility restrictions imposed by the state led to decreased air pollution, known to trigger lung disease exacerbations. In addition, the number of subjects with chronic lung disease was not large enough to represent the actual condition of the general population (Freund et al., 2022; Karya et al., 2021). The latter reason is more acceptable than the first because, in this study, there were only seven patients with a chronic lung disease, while there were 105 patients who did not have a chronic lung disease.

Diabetes mellitus increases 1.9 times the risk of COVID-19 patients experiencing severe symptoms compared to patients without diabetes. However, the bivariate and multivariate analysis results showed no significant relationship between diabetes mellitus and severity. This result is not in line with the research of Wang et al. (2020), which has a p-value of 0.009 (Wang et al., 2020). This study showed that 22 out of 42 patients with diabetes mellitus had been vaccinated. Freund et al. (2022) stated that vaccination is the main protective factor from the risk factors for the severity of COVID-19 patients with diabetes mellitus (Freund et al., 2022).

The government continues to strive to increase public enthusiasm for COVID-19 vaccination. The obstacles to administering this vaccine include public ignorance, fear of adverse events after post-immunization, and various issues or misinformation circulating in the community. Therefore, the government continues to provide proper education and information about the COVID-19 vaccine (Nugraheni & Sulistyawati, 2023).

Due to limited medical record data, we did not classify the degree of hypertension. This study also did not analyze the relationship between the different types of vaccinations used by patients and the severity of their symptoms. The increase in COVID-19 cases at the pandemic's peak caused the government to set a policy so that hospital services prioritize patients with severe or critical symptoms. Therefore, research in a broader community context is highly recommended. This study also overlooked hypertension patients with complete or incomplete immunization status and its association with symptom severity.

4. CONCLUSION

In COVID-19 patients, there is a significant association between the completeness of vaccination status and the severity of symptoms. Patients without complete vaccinations are more likely to experience severe and critical severity. Hypertension is another factor that is significantly associated with symptom severity. Increasing community access to full vaccination is necessary to reduce the possibility of COVID-19 individuals acquiring more severe symptoms and complications. In general, vaccinations are intended to lower a person's

risk of infection, severe symptoms, or serious sequelae. Therefore, pushing for immunization is vital, especially in vulnerable groups. Future studies can be conducted in the general population to describe a wider population. Research to compare different types of vaccines and their effect on patient severity is an exciting theme to research. Research to produce vaccines to reduce the risk of transmission, as well as the severity of a disease, is critical for overcoming numerous infectious diseases and the risk of an outbreak.

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