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The Association Between CoronaVac Vaccine Doses and the Severity of Acute Respiratory Distress Syndrome (ARDS) at The Secondary Referral Hospital in West Nusa Tenggara, Indonesia

Qodrathun Arifia[1], Desak Made Dinda Kartika Utari[1], Melia Fadiansari Suriansyah[1], Rina Lestari[2,3], Metta Octora[3]

Province of Nusa Tenggara Barat General Hospital, Mataram, Indonesia[1]
Pulmonology Department, Province of Nusa Tenggara Barat General Hospital, Mataram, Indonesia[2]
Faculty of Medicine, Mataram University, Mataram, Indonesia[3]

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ABSTRACT

COVID-19 outbreak was first identified in Wuhan, China and spread rapidly throughout the world. COVID-19 can cause fatal comorbidities, especially ARDS. This observational analytic study analyse the association between the dose of CoronaVac vaccination and the severity of ARDS in the Province of NTB General Hospital with a cross-sectional method involving confirmed COVID-19 patients aged 18-59 years whose blood were analysed in the isolation ICU at the Province of NTB General Hospital in the period of March 2021 – March 2022. The data was taken from the subjects' medical records by the consecutive sampling technique and analysed by Spearman test. Total of 51 subject, the male subject was 52.9% and the mean age was 47.64 years. Most subjects had not received vaccination (78,4%), whereas subjects had received the first dose of vaccine (13.7%) and subjects had received the second dose of vaccine (7.8%). More subjects presented with dyspnea (86.3%), cough (80.4%), and fever (60.8%). Hypertension and diabetes mellitus were the main comorbidities (13.7%). Outcomes in this study included dead (47.1%), self-isolated (35.3%), and recovered (17.6%). The mean value of the PaO_2/FiO_2 ratio is 127.21. The doses of CoronaVac vaccination has no significant association with the ARDS severity in subjects who unvaccinated (p=0.93), had received the first dose of vaccine (p=0 .47) or had received the second dose of vaccine (p=0.43) in COVID-19 patients treated in the ICU isolation at the Province of NTB General Hospital.

1. Introduction

Since December 2019, there has been a coronavirus disease 2019 (COVID-19) outbreak which was first identified in Wuhan, China. The spread of the COVID-19 was extremely rapid that it spread throughout the

world [1], [2]. Indonesia had a mortality rate of 9%, the highest in Southeast Asia [3], [4]. The World Health Organization (WHO) declared this outbreak a threat to international health. COVID-19 can cause fatal comorbidities, especially acute respiratory distress syndrome (ARDS) [1], [2]. Based on the Berlin criteria, ARDS is divided into 3 levels based on the oxygenation index (PaO_2/FiO_2), including mild (PaO_2/FiO_2 200-300mmHg), moderate (100-200) and severe 100mmHg [2], [3]. The mortality rate for COVID-19 patients with ARDS is 50%-94%, with the outcome of ARDS patients due to COVID-19 is worse than ARDS patients caused by other diseases. In Indonesia, it has been known that the mortality rate of COVID-19 patients treated in the Intensive Care Unit (ICU) of Dr. Saiful Anwar Hospital, Malang and Karsa Husada Hospital, Batu in November 2020 was 47% (190 patients) to 81.7% (82 patients) [5]. Immune response to SARS-CoV-2 involves innate immune activation and antigen-specific response by B cells and T cells [6].

ARDS is a form of lung tissue injury as an inflammatory response to various causative factors, and is characterized by inflammation, increased vascular permeability, and decreased aeration of lung tissue. In ARDS, there is an increase in capillary permeability due to damage to the vascular endothelium or alveolar epithelium which causes the accumulation of protein-rich fluid in the alveoli, resulting in diffuse alveolar damage and the release of pro-inflammatory cytokines such as Interleukin-1 (IL-1), IL-6 and Tumour Necrosis Factor (TNF). These cytokines attract neutrophils and activate them, resulting in the release of reactive oxygen species and proteases that cause oxidative damage to lung tissue. This fluid accumulation phase is followed by a proliferative phase characterized by the reduction of pulmonary edema, proliferation of type II alveolar cells, fibroblasts, and myofibroblasts, and matrix deposition. Furthermore, ARDS might continue to the fibroproliferative phase or lung resolution might occurs and return the lungs into their normal state [5].

COVID-19 infects individuals of all ages. However, there are two main groups that are at higher risk of severe disease: the elderly, and people with comorbidities such as diabetes mellitus, hypertension, cardiorespiratory disorders, chronic liver disease, and kidney failure. Patients with cancer and patients receiving immunosuppressive drugs, as well as pregnant women are also considered to be at higher risk of developing severe disease when infected [7].

Protection from viral infections is mainly obtained with virus-neutralizing antibodies, where humans gain strong immune protection due to infection or vaccination. Vaccine development is critical with the aim of inducing protective immune responses, especially through virus-neutralizing antibodies specifically for SARS-CoV-2 [6]. In Indonesia, the government has implemented health protocols and urges the public to be vaccinated as soon as possible, one of which is with the CoronaVac vaccine. This vaccine has been shown to be harmless and protective after its third phase of trials in various countries around the world. Based on scientific studies, CoronaVac vaccine is 100% efficient and effective in preventing moderate infections, 77.9% effective in preventing possible mild cases, and has efficacy overall at least 50.4% in Brazil's last trial [8].

2. Materials and Methods

This study is an observational analytic research with a cross-sectional method involving confirmed COVID-19 patients aged 18-59 years whose blood were analysed at the Province of NTB General Hospital in the period March 2021-March 2022. The consecutive sampling was carried out to meet the ideal sample size, where the data was taken from medical records. The inclusion criteria in this study were age 18-59 years old and positive RT-PCR results. The exclusion criteria in this study were cardiovascular disease, kidney injury.

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All of the COVID-19 cases in this study were collected from the isolation ICU in Province of NTB General Hospital. We collected the data of gender, age, CoronaVac vaccination status, comorbidities (hypertension, diabetes mellitus, and asthma), symptoms, status outcomes (died/recovered/self-isolated), and laboratory values (leukocytes, thrombocytes, PaO_2/FiO_2 ratio, D-Dimer, NLR).

CoronaVac vaccination status was divided based on the doses of vaccine received by COVID-19 patients, classified into vaccine dose-0, vaccine dose-1 and vaccine dose-2. Then the severity of ARDS was calculated based on the PaO_2/FiO_2 ratio on blood gas analysis. Based on the oxygenation index (PaO_2/FiO_2), the severity of ARDS was divided into mild with PaO_2/FiO_2 of 200-300mmHg, moderate 100-200, and severe ≤100mmHg.

We utilised the Spearman test to analyse the association between the dose of CoronaVac vaccination and the severity of ARDS. This study has obtained permission and Ethical Clearance from the Research Ethics Commission of the Province of NTB General Hospital, No. 070/18/1649/RSUDP/2022.

3. Results

This study was conducted by collecting data from the medical records of patients treated at the Province of NTB General Hospital from March 2021-March 2022. There were 51 subjects who met the inclusion criteria.

Table 1. The clinical data of the subjects

Variable	n (%)	Mean ± SD	Median (min – max)	*p*
Sex				
Male	27 (52,9)			
Female	24 (47,1)			
Age (year)		47,67 ± 10,6	50 (24 – 59)	0,11
Vaccination Status				
Vaccine dose-0	40 (78,4)			
Vaccine dose-1	7 (13,7)			
Vaccine dose-2	4 (7,8)			
Clinical symptoms				
Dyspnea	44 (86,3)			
Fever	31 (60,8)			
Cough	41 (80,4)			
Sore throat	2 (3,9)			
Cold	10 (19,6)			
Fatigue	11 (21,6)			
Headache	2 (3,9)			
Nausea	9 (17,6)			
Anosmia	7 (13,7)			
Status outcomes				
Dead	24 (47,1)			
Recovered	9 (35,3)			
Self-isolated	18 (17,6)			
Comorbid diseases				
Asthma	5 (9,8)			
Hypertension	7 (13,7)			
Diabetes Mellitus	7 (13,7)			
Laboratory				
Ratio of PaO_2/FiO_2		127,21 ± 144,01		

Leukocytes	14912,35 ±22462,4	10160 (3170 – 164000)	0.000*
Thrombocytes	281556.86 ± 126778.29	258000 (4000 – 701000)	0.072*
Ratio of Neutrophil/ Lymphocytes	12.56 ± 11.02	9,0 (1,00 – 50)	.000*
D-Dimer	3,96 ± 3,67	2,07 (0,13 – 10,00)	.000*
CRP	74,33 ± 46,60	91 (5 – 120)	.000*

SD = standard deviation, min = minimum, max = maximum
*Kolmogorov-Smirnov

From the Table 1, the 51 subjects consisted of 27 male subjects and 24 female subjects with a median age value of 50 years old with a minimum age of 24 years and a maximum of 59 years.

In this study, the data collected from medical records also included the CoronaVac vaccination status, clinical symptoms, comorbid diseases, outcome status, and laboratory results of the subjects.

Out of 51 subjects, 40 subjects had not received the vaccine, 7 subjects had received the first dose of vaccine and 4 subjects had received the second dose of vaccine. In addition, it was revealed that the most clinical symptoms experienced by subjects were dyspnea recorded in 44 subjects (86.3%), followed by cough on 41 subjects (80.4%), fever on 31 subjects (60.8%), fatigue experienced by 11 subjects (21.6%), cold suffered by 10 subjects (19.6%), nausea/vomiting on 9 subjects (17.6%), anosmia on 7 subjects (13.7%), and sore throat on 2 subjects (3.9%).

Moreover, the analysis results of the medical records found that hypertension and diabetes mellitus were the most common comorbid diseases had by the subjects, with as many as 7 subjects (13.7%) had hypertension and diabetes mellitus, while 5 subjects had asthma (9, 8%). Outcome status in this study included 24 subjects (47.1%) were died, 18 subjects (35.3%) were self-isolated, and 9 subjects (17.6%) were declared cured.

This study also displayed the results of laboratory tests carried out on subjects, including the PaO_2/FiO_2 ratio, leukocytes, platelets, neutrophil/lymphocyte ratio, D-Dimer and CRP. It was found out that the mean of PaO_2/FiO_2 ratio was 127.21 ± 144.01. The mean value of leukocytes was 14912.35 ± 22462.4, while the mean value of platelets was 281556.86 ± 126778.29. The mean value of leukocytes and platelets has increased when compared to the normal reference value of the laboratory of the Province of NTB General Hospital.

In the results of the ratio of neutrophils/lymphocytes, obtained a mean of 12.56 ± 11.02. The mean value had increased from the normal reference value. The neutrophil/lymphocyte ratio indicates a disease prognosis with high sensitivity and specificity, where the normal value of NLR <3.3. If the NLR value is >3.3, the probability of developing a more severe disease will increase to 45.1% [9].

Based on the data from Table 1, the mean value of D-Dimer was 3.96 ± 3.67. The mean value had increased above the normal reference value. Likewise, the mean of CRP value had also increased above the normal reference value, which was initially 74.33 ± 46.60.

This study also conducted an analysis on the association between CoronaVac vaccination status and the severity of ARDS. Following are the data on the severity of ARDS in subjects based on the PaO_2/FiO_2 ratio

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and classified based on the subject's vaccination status.

Table 2. Severity Level of ARDS based on the CoronaVac Vaccination status

		Severity level of ARDS			
		Severe ARDS	Moderate ARDS	Mild ARDS	*p**
Vaccination status of CoronaVac	Vaccine dose-0	28	10	2	0,93
	Vaccine dose-1	6	0	1	0,47
	Vaccine dose-2	2	2	0	0,43
Total		36	12	3	51

ARDS = acute respiratory distress syndrome
*Spearman's correlations

The Spearman correlation test showed that the doses of CoronaVac vaccination has no significant association with the ARDS severity in subjects who had not been vaccinated, had received the first dose of vaccine or had received the second dose of vaccine, with *p*-values of p=0.93 (not yet vaccinated), p=0.47 (vaccine dose-1) and p=0.43 (vaccine dose-2), respectively.

There were 40 subjects who had not been vaccinated, of which 28 subjects had severe ARDS, 10 subjects had moderate ARDS, and 2 subjects were with mild ARDS. Of all 7 subjects who had received the first dose of vaccine, as many as 6 subjects had severe ARDS, while 1 subject had mild ARDS. Meanwhile, of the 4 subjects who had received the second dose of vaccine, 2 subjects developed severe ARDS and 2 subjects had moderate ARDS.

4. Discussion

This study is an observational analytic study with a cross-sectional method, carried out by collecting data from subjects' medical records on confirmed COVID-19 patients treated in the ICU isolation room at the Province of NTB General Hospital for the period of one full year from March 2021 to March 2022. The subjects' data included gender, age, COVID-19 vaccination status, clinical symptoms, comorbid disease, outcome status, PaO_2/FiO_2 ratio, leukocytes, platelets, neutrophil-lymphocyte ratio (NLR), D-Dimer and CRP.

This study found that men suffered from COVID-19 more than women. Other studies have also shown the similar result, where COVID-19 sufferers were predominantly male (69%) with an average age of 62 ± 13 years [10]. It was also revealed that gender and age are risk factors that can affect the occurrence of ARDS [1].

Old age is associated with the higher risk of ARDS and death due to a decreased immune system response [11]. 32.9% of COVID-19 patients aged 60 years showed lymphopenia (lymphocytes < 0.8 x 109/L), which indicates the damage of the immune system in the body. In addition, increased neutrophil counts and CRP values in elderly COVID-19 patients indicate an increased inflammatory response [12].

Old age is associated with an increased risk of life-threatening infections. The aging process induces a series of changes that affect the immune system. This age-related vulnerability arises through the development of maladaptive physiological processes that affect an individual's ability to maintain homeostasis when encountering a variety of stressors. This process creates the hallmarks of aging and is associated with age-related susceptibility to stress, also known as homeostenosis [13], [14].

Immune cells mediate the host's responses to viral pneumonia-induced ARDS, including Treg cells with

pro-repair functions. This function is associated with the DNA hypomethylation of the lineage-specific Treg cell. Recent studies have shown the accumulation of toxic metabolites and reactive oxygen species induced by age-related mitochondrial dysfunction can induce epigenetic changes in Treg cells, impairing their pro-repair function and inhibit the resolution of inflammation and the recovery of lung injuries. Monocytes and naive T lymphocytes experience the cellular senescence due to erosion of chromosomal telomeres as the result of continuous replication. Shorter monocyte telomere length in the elderly indicates an age-related decrease in pathogen clearance and TNF- α mediates excessive apoptosis. Along with thymic involution, the age-related reduction in the number of naive T cells poses a barrier to the adaptive immune system from producing antigen-specific memory T cells, including against vaccines [13].

Ultimately, replicative senescence affects a wide range of somatic cells and is associated with a shift toward a basal, chronic pro-inflammatory cytokine secretion, called senescence-associated secretory phenotype (SASP). The accumulation of SASP-like cells throughout aging results in the continuous recruitment and activation of effector immune cells that interfere with local pro- and anti-inflammatory communications of the immune system, inducing tissue damage and inhibiting tissue repair [13].

Epidemiological data from the Chinese Centre for Disease Control (CDC) for COVID-19 showed that the Case Fatality Rate (CFR) of male patients (2.8%) was higher than that of female patients (1.7%). This difference was associated with the differences in immune response by sex and age. Immunological differences by sex contribute to variations in susceptibility to infectious disease, response to viruses, and disease malignancy. In general, women have a stronger and more adaptive immune response than men, which is related to the production of sex hormones as well as the differences in the number of immunity-related genes found on the X chromosome [15].

The most common clinical manifestations in this study were dyspnea, cough, and fever. In another study, it was found that the clinical manifestations that appeared first in COVID-19 patients were fever and cough [1]. The clinical symptoms of COVID-19 varied depending on the degree of disease but the main symptoms were fever (98%), cough, myalgia, dyspnea, headache, diarrhoea, nausea, and abdominal pain [3]. Cough symptoms are usually a dry cough (59.4-82%) due to less sputum production. It occurs because there is less injury to endothelial cells resulting in less exudation [2].

The most common comorbid diseases found in the subjects of this study were hypertension and diabetes mellitus. Hypertension and diabetes mellitus are the most common comorbid diseases in COVID-19 patients who experience ARDS and increase the risk of critical conditions to death [1], [10]. Age (>70 years), gender, hypertension and diabetes are known to be risk factors for ARDS in COVID-19 patients [2]. Other studies have shown that diabetes mellitus alone or in combination with hypertension increases the risk of severe infection; however, hypertension alone confers a slightly increased risk [16].

We have excluded other comorbid diseases such as chronic kidney disease and cardiovascular disease. Patients with kidney disease appear to be at high risk for contracting COVID-19 and developing complications because most are of old ages and have many comorbid illnesses, and some may be taking immunosuppressive drugs for autoimmune disease or kidney transplant failure. Dialysis patients have additional risk factors, including chronic immune dysfunction, the need to go to the hospital for haemodialysis (HD), and sharing rooms with other patients [17].

The mean NLR in the subjects of this study increased when compared to the normal reference value. NLR is an indicator of systemic inflammation. NLR shows disease prognosis with high sensitivity and

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specificity, where the normal value of NLR <3.3. If the NLR value >3.3, the possibility of developing more severe disease will increase to 45.1%. Another study found that increasing age and increasing NLR are associated with the severity of COVID-19 disease and can be biomarkers to assess poor prognosis in COVID-19 patients [9].

The mean D-Dimer and CRP had also increased from the normal reference value in the subjects. In COVID-19 infection, the risk of thromboembolism is thought to be due to abnormalities in coagulation factors. In addition, immobilization and vascular inflammation cause hypercoagulable conditions and endothelial dysfunction triggered by hypoxia or hemodynamic instability. Another study showed a significant increase in D-Dimer results in COVID-19 patients who died in the ICU. Elevated D-Dimer plays an important role in critically ill patients and can be used to monitor the development of critically ill patients [1].

In previous meta-analyses, COVID-19 patients who died showed a significant increase in CRP concentrations compared to recovered patients. CRP is an acute phase protein that is responsible for pathogens through the complement system and enhanced phagocytosis. It has been reported that patients requiring invasive ventilation exhibit elevated inflammatory markers including CRP. This finding made CRP to be a biomarker to assess mortality in COVID-19 [18], [19].

ARDS is the most common complication in the critical phase of COVID-19 with a relatively high mortality rate [20]. Based on the Berlin Criteria, ARDS is defined as acute hypoxemic respiratory failure with a specific cause (such as respiratory viral infection) accompanied by the appearance of bilateral infiltrates on chest x-ray/CT scan to exclude cardiogenic or hydrostatic aetiology [5]. COVID-19-associated ARDS were divided into three categories based on the Berlin Criteria oxygenation index (PaO_2/FiO_2) at 5 cmH_2O PEEP: mild (200 mmHg < PaO_2/FiO_2 < 300 mmHg), mild-moderate (150 mmHg < PaO_2/FiO_2 < 200 mmHg), and moderate-severe (PaO_2/FiO_2 < 150 mmHg) [2], [5].

In this study, the average value of the PaO_2/FiO_2 ratio of the subjects was included in the moderate ARDS category, with the highest number of cases in the severe ARDS category, and almost half of them were declared dead. In a previous study, of 3400 patients treated with COVID-19, 144 developed ARDS either on arrival at the hospital or during treatment. Of these 144 patients, 69 (47.9%) were declared dead in the hospital [16].

ARDS occurs as a result of an acute systemic inflammatory response that can be caused by disorders of the lungs, either directly or indirectly [2]. ARDS is a form of lung tissue injury as an inflammatory response to various causative factors, and is characterized by inflammation, increased vascular permeability, and decreased aeration of lung tissue [5], [21]. Protection from viral infection is mainly obtained with virus-neutralizing antibodies, where humans obtain strong immune protection from infection or vaccination [22].

This study shows that there is no significant association between the CoronaVac vaccination status and the severity of ARDS in COVID-19 patients treated at the Province of NTB General Hospital from March 2021 to March 2022. This condition is not in line with the results of previous studies which stated that compared with unvaccinated controls, individuals who had received the first or second dose of vaccine were less likely to have more than five symptoms in the first week of illness or on admission, and more likely to be asymptomatic, especially those who aged 60 years or older [23].

Although the COVID-19 vaccine has proven to be very effective, its efficacy is not 100%. After receiving a

dose of vaccine, immunity usually develops two weeks after vaccination. Giving a second dose is needed to achieve optimal immunity [24]. This is in accordance with the findings in this study where most of the subjects had not received the COVID-19 vaccination thus the number of hospitalizations due to COVID-19 and disease progression to death was higher. The COVID-19 vaccination is expected to enable some degree of immunity to the new virus variants and is effective in preventing severe cases and deaths [24].

Administration of three doses of vaccine is more of a preventive measure and giving booster doses is results in more protection than administration of the primary series alone. However, the booster was less protective against the Omicron variant compared to the Delta variant, where in-vitro tests showed a potential for evasion of immunity in Omicron [25]. In this study, no subjects had received a booster dose hence the protective effect had not reached its maximum potential, especially for the Omicron variant where the first case was discovered in December 2021 in Indonesia. This study did not perform whole-genome sequencing examinations to differentiate virus variants that infected subjects. Differences in race or ethnicity in the subjects were also suspected of having an influence on the results of this study.

ARDS is partly caused by the host immune response. The immune response to form antibodies takes about two weeks since the COVID-19 vaccination [24]. In this study, antibody levels were not tested, thus we had no idea whether antibodies against SARS-CoV-2 had been formed when patients were treated with COVID-19. It is expected that further study complemented by a serological test for SARS-CoV-2 antibodies could be carried out.

ARDS itself might be caused by various aetiologies that need to be considered by looking at some of the results of the examination. ARDS is usually categorized as the result of direct lung injuries (such as pneumonia) or indirect lung injuries (such as sepsis) [26]. This study discovered that there was leucocytosis found in the subjects. This finding has proven that ARDS may not be purely caused by COVID-19 alone, where coinfection might occur and cause the subject to fall into a septic condition, thus the COVID-19 vaccination status has no significant association.

5. Conclusion

The dose of CoronaVac vaccination was not associated to the severity of ARDS in COVID-19 patients treated in the isolation ward of the Province of NTB General Hospital.

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