Original Research Report

COVID-19 DISEASE SEVERITY AND BLOOD TEST RESULTS IN UNVACCINATED AND VACCINATED PATIENTS AT BHAYANGKARA HOSPITAL, DENPASAR, INDONESIA

Chanif Lutfiyati Muyasaroh*, Ngurah Intan Wiratmini, Anak Agung Sagung Alit Sukmaningsih

Master's Program of Biology, Faculty of Mathematics and Natural Science, Universitas Udayana, Badung, Indonesia

ABSTRACT

The COVID-19 pandemic caused by SARS-CoV-2 is an unprecedented event in human history. Vaccines are a safe, long-term solution for addressing the COVID-19 pandemic. This study aimed to investigate the differences in disease severity and blood test results between unvaccinated and vaccinated COVID-19 patients. This study used an analytical observational method with purposive sampling. A total of 90 COVID-19 patients at Bhayangkara Hospital, Denpasar, Indonesia, were divided into three groups: unvaccinated group (V0), two-dose vaccinated group (Vp), and three-dose vaccinated group (Vb). Primary data were collected from July to December 2022, while secondary data were collected from January 2021 to June 2022. The data were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney test, as well as one-way ANOVA test followed by Tukey's honestly significant difference (HSD) test with a confidence interval (CI) of 95% and α of 5%. The results revealed significant differences in disease severity ($p<0.001$). V0 had a higher percentage of severe (36.7%) and critical (6.7%) symptoms than Vp (severe=10.0%; critical, n=0) and Vb (severe and critical, n=0). The follow-up tests revealed significant differences in disease severity between V0 and Vp ($p<0.001$), V0 and Vb ($p<0.001$), as well as Vp and Vb ($p=0.001$). Blood test results revealed significant differences in lymphocytes ($p=0.005$), monocytes ($p<0.001$), monocyte-to-lymphocyte ratio (MLR) ($p<0.001$), and eosinophils ($p=0.037$). The follow-up tests revealed significant differences in these four indicators between V0 and Vb, in all parameters except for lymphocytes between V0 and Vp, and in lymphocytes only between Vp vs Vb. In conclusion, unvaccinated patients had a higher percentage of severe and critical symptoms than vaccinated patients. The blood test results revealed significant differences in lymphocytes, monocytes, MLR, and eosinophils. Unvaccinated patients had lower lymphocyte counts, higher MLR levels, and higher monocyte counts than vaccinated patients.

Keywords: COVID-19; SARS-CoV-2; vaccine, disease severity; blood test results; public health

***Correspondence:** Chanif Lutfiyati Muyasaroh, Biological Master Study Program, Faculty of Mathematics and Natural Science, Universitas Udayana, Badung, Indonesia. Email: chanifmuyasaroh@gmail.com

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Highlights:
1. This original research report on the differences in disease severity and blood test results between unvaccinated and vaccinated COVID-19 patients is quite novel, as the COVID-19 pandemic was still happening when this study was carried out.
2. This original research report offers information on the advantages of the COVID-19 vaccines and provides data that the public may use as scientific evidence to counter hoaxes.

INTRODUCTION

Disease severity in COVID-19 is often related to the proportion of immune cells in the patient's body. In COVID-19 patients with severe inflammation, there is an increase in the inflammatory response and a decrease in the immune response. These responses are shown in the blood test results, including the leukocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) (Ok et al. 2021, Erdogan et al. 2021). Vaccination is necessary

for COVID-19 management to reduce the number of COVID-19 cases. The COVID-19 vaccines were developed with the objective of forming individual immunity to accelerate the emergence of herd immunity (Saija 2021).

The Indonesian government aimed to get 234.67 million people vaccinated with a complete or primary dose (two-dose vaccination) and a booster. However, according to a report from the Indonesian Ministry of Health, 74.27% of the targeted population was fully vaccinated, and only 28.57% had received a booster shot as of early December 2022 (Indonesian COVID-19 Task Force 2022). A study by Hartono et al. (2022) showed that the number of hoaxes regarding vaccines was known to contribute to low public confidence in the COVID-19 vaccines. Therefore, this study aimed to find scientific evidence about the benefits of COVID-19 vaccines to dismiss hoaxes.

MATERIALS AND METHODS

This paper presents an analytical observational study conducted at Bhayangkara Hospital, Denpasar, Indonesia. The methods for this study were adapted from prior research with modifications (Hanafi et al. 2021, Islas-Vazquez et al. 2022). This study used a purposive sampling technique. COVID-19 patients, who were infected for the first time, older than 18 years, free of comorbid diseases, not pregnant, and had blood tests within 24 hours of hospital admission, served as the samples. Primary data were collected by direct observation of patients during July–December 2022, while secondary data were gathered from the patients' medical records between January 2021 and June 2022.

The samples were divided into three groups: V0 (unvaccinated), Vp (two-dose vaccinated), and Vb (three-dose vaccinated). This categorization followed the methodology of a study by Bakasis et al. (2022). Each group consisted of subjects randomly selected from as many as 30 patients. The patients' disease severity and blood test results were evaluated. The severity of the COVID-19 disease were categorized as asymptomatic, mild, moderate, severe, and critical (Hanafi et al. 2021). In addition, blood tests were used to analyze the erythrocyte, hemoglobin, hematocrit, leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), blood urea nitrogen (BUN), creatinine, and blood urea nitrogen-to-creatinine ratio (BCR) (Mao et al. 2021). Direct observation provided information on the severity of the patients' diseases. The information was then compared to the criteria in the COVID-19 guidelines issued by the Indonesian Ministry of Health (Indonesian COVID-19 Task Force 2022). Blood samples were analyzed in the laboratory of Bhayangkara Hospital, Denpasar, Indonesia. Blood sampling was performed by puncturing superficial veins with a syringe. The blood samples were placed in edetic acid (EDTA) tubes, rested at room temperature for at least 20 minutes, and homogenized for 5–10 minutes with a roller mixer. After inserting the samples into the Swelab Lumi hematology analyzer, the printed results were used to verify the analysis.

The data were analyzed using a One-Way ANOVA test with a Tukey HSD follow-up test to determine if there was a normal distribution and homogeneous variance. However, if the data were not normally distributed and had a non-homogenous variance, analysis would be performed using the Kruskal-Wallis test with the Mann-Whitney follow-up test (Cleophas & Zwinderman 2016, Lee 2022). All statistical tests were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), with a 95% confidence level and a 5% tolerable error. A result of $p<0.05$ was considered significant.

RESULTS

This study involved 90 COVID-19 patients hospitalized at the Bhayangkara Hospital, Denpasar, Indonesia. The patients consisted of 52 men (58%) and 38 women (42%). Mild COVID-19 patients were those having specific symptoms (upper respiratory infection symptoms) and unspecific symptoms (e.g., anosmia, ageusia, indigestion) without any signs of hypoxia. On the other hand, moderate COVID-19 patients were those with pneumonic symptoms and SpO2>93% while breathing room air. Severe COVID-19 patients were those having pneumonic symptoms with a respiration rate of >30 breaths/minute, severe respiratory distress syndrome, or SpO2<93% while breathing room air. Critical COVID-19 patients were those with acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions requiring life support such as mechanical ventilation or vasopressor therapy.

After classifying the patients according to their disease severity, the total number of patients in each group was counted. Statistical analyses were conducted for each group. The obtained results are shown in Tables 1 and 2.

As shown in Table 1, the booster-vaccinated group had the highest percentage of mild symptoms with

no severe or critical symptoms. Critical COVID-19 symptoms were only found in V0, and severe COVID-19 symptoms were found in V0 and Vp.

Tabel 1. The results of the Kruskal-Wallis test analysis of the differences in disease severity.

Severity	Groups			p
	V0 (n=30)	Vp (n=30)	Vb (n=30)	
Mild	2 (6.7%)	11 (36.7%)	24 (80%)	<0.001
Moderate	15 (50.0%)	16 (53.3%)	6 (20%)	
Severe	11 (36.7%)	3 (10.0%)	0 (0%)	
Critical	2 (6.7%)	0 (0%)	0 (0%)	

Tabel 2. The results of the Mann-Whitney test analysis of the differences in disease severity.

	V0 vs Vp	V0 vs Vb	Vp vs Vb
Disease severity	<0.001	<0.001	0.001

Table 3. Mean differences from the analysis of blood test results with the Kruskal-Wallis test.

Parameters	Groups			p
	V0 (n=30)	Vp (n=30)	Vb (n=30)	
Hb	14.44±1.98	13.97±1.69	14.43±1.40	0.283
Leukocyte	7.63±2.94	6.72±2.64	7.26±1.90	0.248
Neutrophil	5.30±2.73	4.70±2.67	5.03±1.65	0.399
Lymphocyte	1.31±0.58	1.52±0.59	1.76±0.51	0.005
NLR	4.73±2.89	3.58±2.57	3.02±1.13	0.056
Monocyte	0.87±0.45	0.47±0.42	0.48±0.28	<0.001
MLR	0.82±0.69	0.35±0.33	0.28±0.15	<0.001
Eosinophil	0.09±0.10	0.13±0.09	0.22±0.38	0.037
Basophil	0.04±0.05	0.05±0.07	0.03±0.02	0.629
Platelet	196.00±59.97	232.10±76.86	222.07±45.66	0.142
PLR	173.29±76.60	171.75±78.50	137.46±52.56	0.090
Hematocrit	39.70±5.41	40.85±5.05	42.36±4.04	0.112
SGOT	40.57±30.15	40.27±32.00	32.67±16.42	0.518
SGPT	40.83±27.67	43.63±46.50	33.23±20.55	0.384
Urea	22.70±7.81	21.67±7.25	22.30±6.56	0.345
Creatinine	1.02±0.21	0.95±0.28	0.99±0.22	0.398

Table 2 shows the results of the follow-up test. There were significant differences in disease severity between V0 vs. Vp, V0 vs. Vb, and Vp vs. Vb. In addition, the mean results of the blood tests were analyzed statistically for those three groups. Table 3 shows the average blood test result in each group according to a number of parameters and the p-value for each parameter. The data obtained from the parameters shown in Table 3 were not normally distributed and had a non-homogenous variance. As shown in Table 5, analyses using the Kruskal-Wallis and Mann-Whitney tests were necessary for the follow-up tests.

Two parameters shown in Table 4 were normally distributed and had homogeneous variance. A One-Way ANOVA test was conducted for these parameters, and there were no significant differences in the results. Therefore, no follow-up test was conducted.

Table 4. Mean differences from the analysis of blood test results with One-Way ANOVA test.

Parameters	Groups		
	V0 (n=30)	Vp (n=30)	Vb (n=30)
Erythrocyte	4.81±0.62[a]	4.92±0.60[a]	4.93±0.58[a]
BCR	23.03±9.13[a]	27.89±25.52[a]	23.40±7.99[a]

Note: values with the same superscript ([a]) were not significantly different.

The blood test results for lymphocytes, monocytes, MLR, and eosinophils among the unvaccinated, 2-dose vaccinated, and 3-dose vaccinated groups were significantly different (p=0.005; p<0.001; p<0.001, and p=0.037, respectivelyOn the other hand, the other parameters showed no significant differences in the blood test results (p>0.05). There was a trend of decreasing lymphocytes and eosinophils as well as increasing MLR and monocytes in the unvaccinated group compared to the vaccinated group (Table 3). The follow-up test results for parameters with significantly different results (p<0.05) are shown in Table 5.

Tabel 5. Mean differences from the analysis of lymphocyte, monocyte, MLR, and eosinophil parameters with the Mann-Whitney test.

	V0 vs Vp	V0 vs Vb	Vp vs Vb
Lymphocyte	0.192	0.002	0.031
Monocyte	<0.001	<0.001	0.466
MLR	<0.001	<0.001	0.679
Eosinophil	0.047	0.016	0.706

Table 5 shows that the monocyte, MLR, and eosinophil parameters between V0 and Vp were significantly different, while the lymphocyte parameter was not. All indicators between V0 and Vb were significantly different. The lymphocyte parameter between Vp and Vb was significantly different, while the others were not.

DISCUSSION

Disease severity indicates the severity of the symptoms experienced by the patient. In this research, unvaccinated patients were more likely to experience moderate, severe, or critical symptoms compared to vaccinated patients. This result is in line with the research conducted by Antonelli et al. (2022). A significant difference in disease severity was caused by specific immunity against the COVID-19 infection in the vaccinated patients.

Lymphocyte count in the unvaccinated COVID-19 patients was lower compared to the vaccinated patients, as shown in Table 3. Lymphopenia, which is defined as a lymphocyte count <1.5x109/L, is common in severe or critical COVID-19 patients (Zhao et al. 2020, Zhang et al. 2020). It occurs due to the binding of Fas ligand (FasL) and Fas receptors (FasR) on damaged cells. The damaged cells can induce programmed cell death, thus decreasing blood lymphocyte levels (Mazzoni et al. 2020). Infections or other conditions affecting the blood can cause a decrease in the concentration of lymphocytes in the blood. The COVID-19 infection depletes and inhibits the expansion of T lymphocyte cells (Diao et al. 2020, Ouyang et al. 2020). It is possible for SARS-CoV-2 to cause infection in vitro because, although in a low level, human T cells also contain mRNA of the ACE2 receptor (Tavakolpour et al. 2020). The sequestration and infiltration of peripheral T lymphocytes can also cause lymphopenia. Lungs, digestive tract, and lymphatic tissue are some of the organs that have the potential to be affected (Huang & Pranata 2020). In this research, lymphopenia was most prevalent in the unvaccinated group, which had a higher percentage of severe and critical symptoms than the vaccinated group. These findings are in line with those of a prior study conducted by Huang & Pranata (2020). The study showed that vaccinated patients who had already developed an adaptive immune system were less susceptible to lymphopenia than unvaccinated patients.

In this study, there was a significant difference in monocyte counts. The unvaccinated group was more likely to experience monocytosis, an increase in monocytes in the blood >0.6x10^9/L (Mao et al. 2021). In severe SARS-CoV-2 infections, lung damage has been reported as increased numbers of monocytes and decreased numbers of lymphocytes in the blood. In the previous study of the blood immunity characteristics of COVID-19 patients, it was found that there was an increase in pro-inflammatory monocytes and IL-6 levels in severe and critical COVID-19 patients (Zhou et al. 2020). Another previous study showed that more than 50% of COVID-19 patients had monocytosis. Patients with severe or critical COVID-19 symptoms have an even higher risk of developing monocytosis (Mao et al. 2021, Porto et al. 2022). It is in line with the results of this study that showed the unvaccinated group had the highest percentage of severe and critical symptoms, thereby having a higher risk of experiencing monocytosis. In unvaccinated patients, adaptive immunity has not been formed optimally, and there is an excessive inflammatory response characterized by an increase in pro-inflammatory cytokines that causes cytokine storms (Zhou et al. 2020).

Referring to the two parameters above (lymphocytes and monocytes), the MLR indicator also had significant differences in this research. MLR is an inflammatory marker used to predict the severity of COVID-19 (Citu et al. 2022). MLR has a specificity of 90% for distinguishing COVID-19 patients from healthy people. In addition, MLR has a sensitivity of 75.79% for identifying the differences (Peng et al. 2020). Previous studies revealed that the MLR value in severe-critical COVID-19 patients typically increased significantly in comparison to mild-moderate COVID-19 patients. The MLR value was much higher in patients who were dying (Sun et al. 2020, Ertekin et al. 2021). The Mann-Whitney follow-up test revealed that the unvaccinated group in this research had the highest percentage of severe and critical symptoms as well as the highest MLR value.

Another parameter that showed a significant difference in the results of this study was eosinophils. Eosinophils were originally identified as the main effectors of allergies, but now these cells have been shown to have antiviral activity and function to enhance the immune response and suppress inflammation (Lindsley et al. 2020, Hernaningsih 2021). In spite of the significant difference, the values of eosinophils in all groups were in the normal range. However, the absence of eosinophils could be used to identify COVID-19 cases, especially those that have a higher probability of death, so that clinicians can start therapy earlier (Tanni et al. 2020).

Strength and limitations

The samples in this study were collected in almost similar conditions, thereby reducing research bias. The results of the study clearly illustrated the differences in disease severity and blood test results between unvaccinated and vaccinated patients. Therefore, the information in this paper can provide a scientific picture of the importance of COVID-19 vaccination for the public. However, the limitation of this research was that the number of research samples was limited. This was a unicentric study conducted in one hospital and covered only a small geographic area.

Due to the limitations of this research, further research is needed with a larger and more diverse number of samples and considering comorbid diseases. Comprehensive research also needs to be carried out by adding research variables (such as the type of vaccine) and data on anti-COVID antibody levels. This research still provides a potential opportunity in terms of knowledge and data that can be used as scientific information for the public.

CONCLUSION

Unvaccinated patients had a higher percentage of severe and critical symptoms than vaccinated patients. In addition, the number of lymphocyte counts in the unvaccinated group were lower, while the MLR levels and the number of monocyte counts were higher in the vaccinated group. However, the number of eosinophils in all groups was still within normal limits.

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Conflict of interest

None.

Ethical consideration

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None.

Author contribution

CLM conceptualized the study, wrote and prepared the original draft, and collected the data. NIW conceptualized the study, developed the methodology, and reviewed and edited the manuscript. AASAS provided validation for the study. All authors have read and agreed to the final version of the manuscript for publication.

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