

## Steroid impact on the efficacy and safety of SARS-CoV-2 vaccine: a systematic review



Pujo Prawiro Negoro<sup>1\*</sup>, Gatot Soegiarto<sup>1,2</sup>, Laksmi Wulandari<sup>3</sup>

### ABSTRACT

**Background:** The COVID-19 vaccine has become the utmost protection against the pandemic, with billions of doses has been used across the globe. Immunosuppression has been one of the leading issues in the vaccination program, one of which should not be handled lightly is the use of the steroid. Thus, this systematic review is aimed to explore the impact of steroid use on the efficacy and safety of the COVID-19 vaccine.

**Methods:** The systematic review is conducted based on the PRISMA guideline by conducting a literature search and screening process through several databases (PubMed, ScienceDirect, Scopus, and EBSCOHost) based on the predetermined PICO criteria. Original articles (Controlled trial or cohort) on the use of steroids in healthy or non-immunocompromised or autoimmune patients were included. The included articles were then assessed for risk of bias using the ROBINS-I tool.

**Results:** 6,857 articles were screened, with two articles included for the final analysis. The results show a non-significant impact of steroid use on the vaccine efficacy based on seropositivity and antibody count. However, steroid use is related to milder adverse effects and symptoms.

**Conclusion:** Steroid is not associated with lower response to the COVID-19 vaccine. Further research on the dose-dependent response to steroid use should be conducted.

**Keywords:** COVID-19, steroid, systematic review, vaccine.

**Cite This Article:** Negoro, P.P., Soegiarto, G., Wulandari, L. 2023. Steroid impact on the efficacy and safety of SARS-CoV-2 vaccine: a systematic review. *Bali Medical Journal* 12(1): 826-830. DOI: 10.15562/bmj.v12i1.3947

### INTRODUCTION

The current management in protecting against COVID-19 is mainly vaccination. More than 10 billion doses of vaccination have been administered worldwide, and 64.1% of the population in South and East Asia have completed primary COVID-19 vaccination.<sup>1</sup> Despite the vaccine hesitancy of more than 25%, the program was considered successful in lowering the incidence rate of COVID-19.<sup>2</sup> Various managements, from novel therapies to new approaches in management such as home visits and quarantine is, also set to control the pandemic.<sup>3,4</sup> Based on the initially identified Wuhan lineage virus, the SARS-CoV-2 spike protein is the primary target antigen in most COVID-19 vaccines.<sup>1,5</sup> factors might affect the efficacy of COVID-19 vaccine, for instance, chronic conditions such as hypertension.<sup>6</sup> Particularly, the immune response is also attributable to autoimmune disease or immunosuppression due to medication.

Immunosuppression can interfere with the work of vaccination. Thus, patients with chronic inflammatory diseases are one of the populations that require special attention in determining eligibility for vaccination. This is

due to various chronic inflammatory diseases using immunosuppressive agents as their primary management, such as glucocorticoids, antimetabolites, tumor necrosis factor inhibitors, etc. The Spine Intervention Society Fact Finder published recommendations to discontinue steroid use two weeks before injection of the COVID-19 vaccine and one week after receiving a vaccination.<sup>7</sup> In addition, the publication by Shen C et al. concluded that immunosuppressed patients who had been vaccinated remained more susceptible to COVID-19 infection than non-immunosuppressed patients.<sup>8</sup> However, The American Society of Pain and Neuroscience publication concluded that there was no significant effect of administering steroids on COVID-19 vaccination.<sup>8,9</sup>

The IDSA Clinical Practice Guidelines for Immunity Host Vaccination indicate that at doses up to 20 mg/day of prednisone or equivalent, the response to an inactivated vaccine cannot be suppressed. Thus, these patients can receive the vaccine safely. With a prednisone dose of fewer than 20 mg/day, the patient does not have a compromised immune system and has a sufficient immune response to receive the vaccine. However, due to the risk of worsening symptoms

<sup>1</sup>Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;

<sup>2</sup>Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;

<sup>3</sup>Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;

\*Corresponding author:

Pujo Prawiro Negoro;  
Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia;  
[Pujopn@gmail.com](mailto:Pujopn@gmail.com)

Received: 2022-11-29

Accepted: 2023-01-15

Published: 2023-02-23

and disease recurrence, reducing the dose of corticosteroids over a period is not an option in certain conditions. For this reason, this review discusses to what extent it is safe to reduce the dose of steroids that do not cause a decreased response to vaccination.<sup>10,11</sup>

## METHODS

This systematic review is conducted by adhering to the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis).<sup>12</sup> The search process was also conducted based on the PRISMA flowchart on the literature search and screening process.

### Literature Search

All authors start the searching process using the predetermined keyword based on the PICO (Patient, Intervention, Control, Outcome) criteria of the topic, which entails as follows: Patients underwent COVID-19 vaccination (Patients), Corticosteroids or immunosuppressants (Intervention), Placebo (Control), Vaccinations outcome, i.e., antibody count, susceptibility rate, seroconversion rate (Outcome). The PICO criteria were then extrapolated into several keywords for the databases. If available, MeSH terms were also then used for the search process. The keywords or search queries are used, as stated in [Table 1](#). The study search was then conducted across the selected scientific databases, such as PubMed, ScienceDirect, ProQuest, and Scopus. Literature considered related to the topic was also included if it was found through hand-searching on references.

### Study Selection

The selection process was conducted against predetermined inclusion and exclusion criteria. Studies which considered eligible based on PICO criteria, with original study design, were considered for inclusion. Meanwhile, studies not retrievable for full-text and patient populations with immunosuppressive or immunostimulant medication will be excluded.

### Risk of Bias Assessment

The risk of bias assessment will be conducted using the Cochrane Risk of Bias Tool 2.0 for the randomized studies and ROBINS-I for non-randomized

**Table 1.** Search queries based on PICO criteria for the literature search process.

Scientific Databases	Keywords or Search Queries
PubMed	((((corticosteroid [MeSH Terms] OR "prednisone" OR "prednisolone") OR (dexamethasone[MeSH Terms])) OR (agents, immunosuppressive[MeSH Terms]) AND ("COVID-19" OR "SARS-CoV-2") AND ("Vaccine" OR "Vaccination")) AND (vaccine[MeSH Terms])
ScienceDirect	(Corticosteroid OR (immunosuppressive OR immunosuppressant)) AND ("COVID-19" OR "SARS-CoV-2") AND ("Vaccine" OR "Vaccination")
EBSCOHost	(Corticosteroid OR (immunosuppressive OR immunosuppressant)) AND ("COVID-19" OR "SARS-CoV-2") AND ("Vaccine" OR "Vaccination")
Scopus	(Corticosteroid OR "prednisone" OR "prednisolone" OR dexamethasone) OR (immunosuppressive OR immunosuppressant) AND ("COVID-19" OR "SARS-CoV-2") AND ("Vaccine" OR "Vaccination")

studies.<sup>13</sup> Each included study was then assessed based on the criteria. Those with a low risk of bias or concerns with objective evaluation from all authors will be included in the data extraction and analysis.

### Data Extraction

The data was extracted using Microsoft Excel 365 (Illinois, USA). The data were extracted through a spreadsheet which then produced tables on the study characteristics and notable outcomes, particularly the used corticosteroid and immunosuppressants with their respective dose and the outcome of vaccination such as seroconversion rate or antibody count. Analysis of booster and non-booster vaccination were also made into subgroups to determine the difference between the two vaccinations.

## RESULTS

### Literature research results

Of the 1700 abstracts screened, two studies published up to 2022 met the inclusion criteria, as illustrated in [Figure 1](#). A research group published one study in Japan, and the other study was from South Korea.

### Methodological quality evaluation

Two of the included studies adopted the prospective cohort method. All studies have a low bias in participant selection, deviation from the intended intervention, data extraction, outcome measurement, and selection of reported outcomes.

Due to the classification of confounders and interventions, Nakajima et al. have a moderate bias because the treatment provider knew that the participants were asthmatic or rhinitis patients. Meanwhile, in the study of Yang J et al., participants had no underlying condition, and treatment providers were blinded. In general, all the included studies were eligible with low to moderate bias, as seen in [Table 2](#).<sup>14,15</sup>

### The characteristics of the included studies

Two included studies have a total of 225 participants. The median ages of the two studies were 44 and 60 years, respectively. The study by Nakajima T et al. used the vaccine type BNT162b2 (Pfizer), as did Yang J et al. However, Yang J et al. also used another type of vaccine, ChAdOx1 nCoV-19 (Oxford/Astra Zeneca). In addition, Yang J et al. studied the first and second doses, while Nakajima T et al. studied only the second dose. The two studies also examined different steroids; the inhaled type was studied by Yang J et al., while Nakajima T et al. studied the oral type.<sup>14,15</sup> The baseline characteristics of participants are shown in [Table 3](#).

### Association between steroid use and COVID-19 vaccine efficacy

The two included studies measured their outcome in different ways. Nakajima T et al. compared antibody titers of steroid users with a control group not taking steroids, while Yang J et al. compared the reactogenicity and immunogenicity

of the intervention and control groups. Reactogenicity was assessed locally or systemically. Local reactions assessed include pain, redness, and swelling. While the systemic reactions assessed include fever, chill, myalgia, arthralgia, fatigue, headache, vomiting, and diarrhea. As a result, the pain was significantly higher

compared to the BNT group, while side effects were significantly lower compared to the ChAd group (without prednisolone)—less cold, fatigue, myalgia, headache, or need for medication. Yang J et al. also assessed the seropositive rate with a seropositive rate of 100% (14/14) in the intervention group, while the control

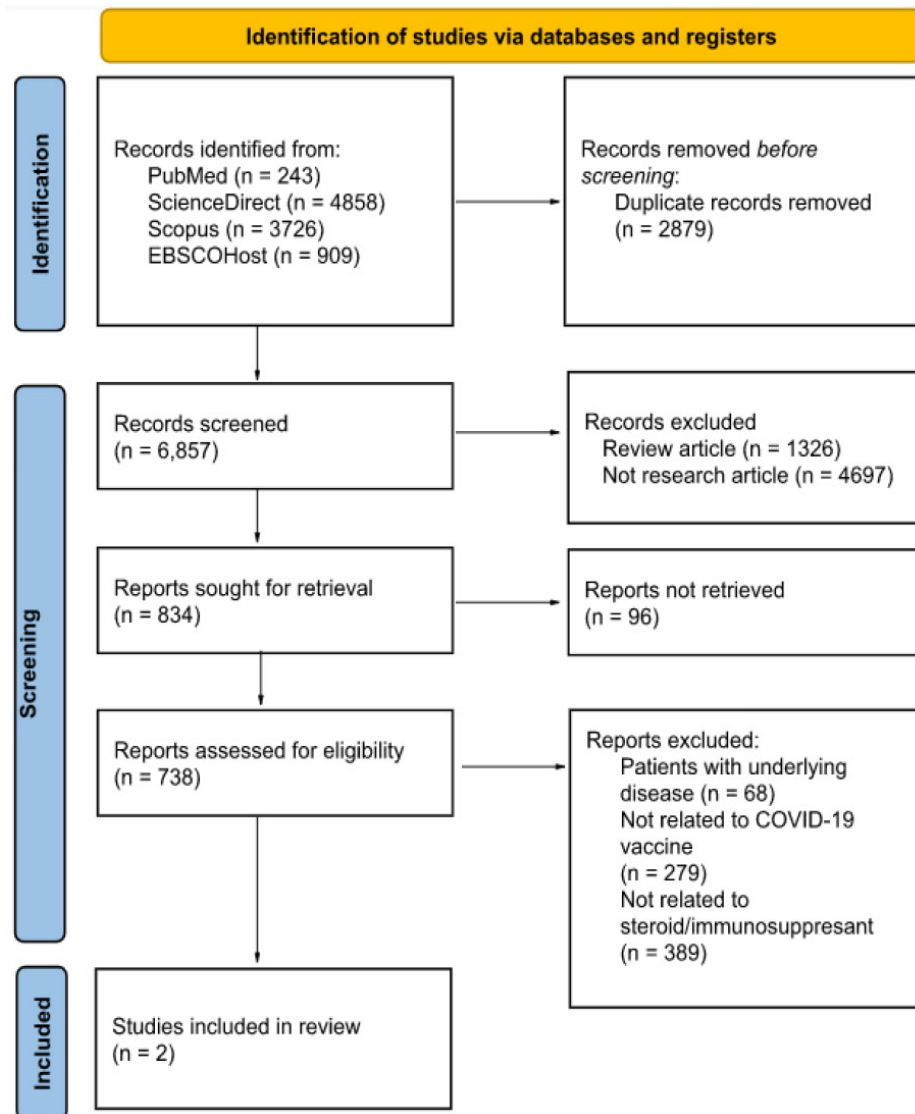
group was 98.5% (23/24) and 100% (29/29) in the Chad and BNT groups, respectively.<sup>14,15</sup>

Both studies assessed antibody levels. In the study of Nakajima T et al., higher antibody levels were found in the ICS user group (572 u/mL) than in the control group (454 u/ml) (p=0.00258). In addition, Yang et al. found antibody levels were higher in the ChAdPd group compared to the ChAd and BNT groups (3.149 ± 3.249 vs. 0.816 ± 1.498 and 0.878 ± 0.608, respectively), with higher rates based on positive margins (64.3% vs. 30% and 50%, respectively). Regarding steroid doses and their effect on vaccines, Nakajima T et al. found no difference in antibody titer between none, middle, and high doses [OR=1,040 (0.668–1.610), p-value: 0.868].<sup>14,15</sup>

**DISCUSSION**

To our knowledge, this study is the first to review the evidence regarding the effect of steroids on antibody levels and the relationship between steroid dose on the efficacy of the COVID-19 vaccine. COVID-19 has been wreaking havoc the society with its high mortality and severity with various risk factors to increase the burden of its disease.<sup>16</sup> The various need-to-know factors in the vaccination as the main means of protection is also essential.

Previous studies do not have a consensus on whether steroids interfere with vaccine efficacy. A previous study reviewed six studies on steroid use and their effect on vaccines, the results of which two studies showed steroid use had no suppressive effect on the immune system and interfered with vaccine action.<sup>9,17,18</sup> However, two studies showed mixed findings. Naito M et al. found that patients taking dexamethasone instead of prednisolone had elevated IgG after



**Figure 1.** PRISMA flowchart of literature screening.

**Table 2.** Risk of bias of the included studies.

Study	Bias due to confounding	Bias in the selection of participants for the study	Bias in the classification of interventions	Bias due to deviations from the intended interventions	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of the reported result	Overall bias
Nakajima, 2022 <sup>14</sup>	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Yang, 2021 <sup>15</sup>	Low	Low	Low	Low	Low	Low	Low	Low

**Table 3. Characteristics of the included studies.**

Study	Sample Size	Median Age	Gender (M/F)	Vaccine Type/Dose	Type of Steroid	Number of Dosages	Follow-up Duration/Study Location
Nakajima et al., 2022. <sup>14</sup>	211	60	68/34	BNT162b2 (Pfizer)/ 2nd dose	Inhaled corticosteroids (Budesonide & Fluticasone)	Budesonide: Low dose (250–499 mcg/day), medium dose (500–1199 mcg/day), and high dose (> 1200 mcg/day)  Fluticasone: low-dose (100–299 mcg/day), medium-dose (300–499 mcg/day), and high-dose (> 500 mcg/day)	Four months/ Hyogo, Japan
Yang et al., 2021. <sup>15</sup>	14	44	2/12	BNT162b2 (Pfizer) A n d ChAdOx1 nCoV-19 (Oxford/ A s t r a Zeneca)/ 1st dose and 2nd dose	Low-dose corticosteroid agents (oral prednisolone or methylprednisolone)	Oral prednisolone 5 mg; Oral methylprednisolone 4 mg; taken with 1t bid, 1t tid, or 2t bid for up to 5 days	12 weeks/ Seoul, South Korea

vaccination.<sup>19</sup> Steentoft J et al. showed that patients who continued steroid use and those who started steroids after vaccination significantly increased antibody titers.<sup>20</sup> Meanwhile, one study showed an association between intra-articular steroid injections and an increase in influenza in vaccinated patients, indicating steroids caused a decrease in vaccine efficacy. The clinical effect of steroids on COVID-19 vaccination is not yet fully understood. However, at the cellular level, glucocorticoid receptors are involved in transactivation, DNA binding, ligand binding, and post-transcriptional and translational enhancement. In addition, dexamethasone suppresses ribosomal proteins and translation initiation factors.<sup>9,21,22</sup>

Our systematic review of two studies indicated that steroid use before COVID-19 vaccination showed no significant effect on vaccine efficacy. In both studies, Nakajima T et al. and Yang J et al. showed higher antibody levels in steroid users than in the control group. In addition, Yang J et al. also found that the seropositive rate of steroid users reached 100%. However, both studies used oral and inhaled steroids, and many previous

studies found a negative association with steroid injection. The largest study to examine the association between steroid use and vaccination was conducted by Sytsma TT et al., which retrospectively examined 15,068 patients taking steroid injections.<sup>23</sup> The result of this study was that patients who used steroid injections had a higher risk of influenza even though they had received the vaccine compared to the control group.<sup>9,14,15</sup>

In general, doses of steroids considered safe for receiving vaccines follow the ACIP (Advisory Committee on Immunization Practices) recommendations which suggest doses of more than 20 mg per day for more than 14 days on prednisone use may impair the body's immune response. Meanwhile, according to the 2013 IDSA recommendations, vaccines should be given before immunosuppression. The rule is that live vaccines are given four weeks before immunosuppression and not until two weeks after.<sup>11</sup> Meanwhile, the inactivated vaccine was given two weeks before immunosuppression. Nakajima T et al. found no significant association between steroid dose and COVID-19 vaccine efficacy in their study.<sup>14</sup> Nakajima T et al. looked at the relationship between

increased antibody titers by comparing three dose levels. The dose of budesonide was divided into low (250–499 mcg/day), medium (500–1199 mcg/day), and high (>1200 mcg), while fluticasone doses were divided into low (100–299 mcg/day), medium (300–499 mcg/day), and high (>500 mcg/day).<sup>14</sup> Different types of steroids can be one of the factors that lead to different conclusions.<sup>9</sup> More research on the use of inhaled steroids and their effect on vaccination is needed to support the study of Nakajima T et al.<sup>14</sup> The use of other management in increasing the efficacy and immune response of the vaccine, such as using traditional herbs or other medication, is also welcomed in boosting the success of the vaccine program.<sup>24–26</sup> Our study has several limitations. First, the number of participants they are limited to the Asian race. Second, the form of steroid used was different in the two studies.

## CONCLUSION

Corticosteroid use does not affect the immunogenicity of the COVID-19 vaccine. In addition, there is no consensus on the optimal dose of steroids as a



condition for receiving the COVID-19 vaccination. Further research on the effect of steroid use on the immunogenicity of COVID-19 is still needed.

## CONFLICT OF INTEREST

The authors declare no conflict of interest in the making of this manuscript.

## ETHICAL CONSIDERATION

No ethical clearance is needed as we conduct a study of the literature.

## FUNDING

The authors are responsible for the study's funding without the involvement of a grant, scholarship, or any other funding resource.

## AUTHOR CONTRIBUTION

PPN was involved in writing the manuscript. GS and LW supervised and revised all manuscripts. All authors prepare the manuscript and agree for this final version of the manuscript to be submitted to this journal.

## REFERENCES

- SEARO. Boost COVID-19 vaccination coverage: WHO. World Health Organization. 2022.
- Fajar JK, Sallam M, Soegiarto G, Sugiri YJ, Anshory M, Wulandari L, et al. Global Prevalence and Potential Influencing Factors of COVID-19 Vaccination Hesitancy: A Meta-Analysis. *Vaccines* 2022;10(8):1356.
- Lusida MAP, Salamah S, Jonatan M, Syamlan AT, Bandem IKMP, Rahmania AA, et al. The Impact of Facilitated Quarantine on Mental Health Status of Non-Severe COVID-19 Patients. *Disaster Med Public Health Prep.* 2022;16(5):1751-1752.
- Widjaja SS, Jayalie VF, Rusdiana R. Strengthening Palliative and Home Care Service During COVID-19 Pandemic in Developing Country: A Single Institution Report. *Open Access Maced J Med Sci.* 2022;10(E):1012-1015.
- Zeng B, Gao L, Zhou Q, Yu K, Sun F. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. *BMC Med.* 2022;20(1):1-15.
- Soegiarto G, Wulandari L, Purnomosari D, Dhia Fahmita K, Ikhwan Gautama H, Tri Hadmoko S, et al. Hypertension is associated with antibody response and breakthrough infection in health care workers following vaccination with inactivated SARS-CoV-2. *Vaccine.* 2022;40(30):4046-4056.
- Streetman DD. Impact of immunosuppressants on COVID-19 vaccine response. 2021. [Cited 13<sup>th</sup> October 2022] [Available from: [https://www.pharmatimes.com/web\\_exclusives/Impact\\_of\\_immunosuppressants\\_on\\_COVID-19\\_vaccine\\_response\\_1372703](https://www.pharmatimes.com/web_exclusives/Impact_of_immunosuppressants_on_COVID-19_vaccine_response_1372703)].
- Shen C, Risk M, Schioppa E, Hayek SS, Xie T, Holevinski L, et al. Efficacy of COVID-19 vaccines in patients taking immunosuppressants. *Ann Rheum Dis* 2022;81(6):875-880.
- Chow RM, Rajput K, Howie BA, Varhabhatla N. The COVID-19 vaccine and interventional procedures: Exploring the relationship between steroid administration and subsequent vaccine efficacy. *Pain Pract.* 2021;21(8):966-973.
- Shokouhi S, Hakamifard A. COVID-19 vaccine and corticosteroids: A challenging issue. *European Journal of Inflammation* 2021;19:1-2.
- Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis.* 2014;58(3):309-318.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;88:372.
- Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Nakajima T, Nagano T, Miyata Y, Murakami S, Mitsuyuki S, Funakoshi Y, et al. Inhaled corticosteroids do not affect the antibody titer against the SARS-CoV-2 spike protein in BNT162b2 mRNA vaccinated patients. *Allergy, Asthma Clin Immunol.* 2022;18(1):1-6.
- Yang J, Ko JH, Baek JY, Hong J, Ha S, Lee B, et al. Effects of Short-Term Corticosteroid Use on Reactogenicity and Immunogenicity of the First Dose of ChAdOx1 nCoV-19 Vaccine. *Front Immunol.* 2021;12:744206.
- Mudatsir M, Fajar JK, Wulandari L, Soegiarto G, Ilmawan M, Purnamasari Y, et al. Predictors of COVID-19 severity: a systematic review and meta-analysis. *F1000Research.* 2021;9(9):1-26.
- Inoue S, Shibata Y, Takabatake N, Igarashi A, Abe S, Kubota I. Influence of corticosteroid therapy on the serum antibody response to influenza vaccine in elderly patients with chronic pulmonary diseases. *EXCLI J.* 2013;12:760-765.
- De Roux A, Marx A, Burkhardt O, Schweiger B, Borkowski A, Banzhoff A, et al. Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly COPD-patients. *Vaccine.* 2006;24(10):1537-1542.
- Naito M, Itoh K, Komatsu N, Yamashita Y, Shirakusa T, Yamada A, et al. dexamethasone did not suppress immune boosting by personalized peptide vaccination for advanced prostate cancer patients. *Prostate.* 2008;68(16):1753-1762.
- Steenoft J, Konradsen HB, Hilskov J, Gislason G, Andersen JR. Response to pneumococcal vaccine in chronic obstructive lung disease--the effect of ongoing, systemic steroid treatment. *Vaccine.* 2006;24(9):1408-1412.
- Herawati S, Kandari Y, Mulyantari NK, Prabawa PY. Correlation of Neutrophil to Lymphocyte Ratio with Interleukin-10 in Diagnosis and Monitoring of Coronavirus Disease-19 Patients. *Open Access Maced J Med Sci.* 2022;10(B):63-66.
- Pranata S, Vranada A, Armyati Y, Samiasih A, Aisah S, Kurnia A, et al. Inflammatory markers for predicting severity, mortality, and need for intensive care treatments of a patient infected with covid-19: a scoping review. *Bali Medical Journal.* 2023;12(1):324-330.
- Sytsma TT, Greenlund LK, Greenlund LS. Joint Corticosteroid Injection Associated With Increased Influenza Risk. *Mayo Clin proceedings Innov Qual outcomes.* 2018;2(2):194-198.
- Widjaja SS, Rusdiana R, Amelia R. Curcumin: Boosting the immunity of COVID-19-vaccinated populations. *J Adv Pharm Technol Res.* 2022;13(3):187-190.
- Ansori I, Riefani S, Nurrasyidah I. The Correlation of Rapid Antibody Results with SARS-CoV-2 PCR in COVID-19 Patients in Ulin General Hospital Banjarmasin. *Jurnal Respirasi Unair.* 2021;7(3):100-105.
- Hasanudin H, Sukartini T, Makhfudli M. The Effectiveness of Pulmonary Rehabilitation on Pulmonary Function among Adult Patient of COVID-19 Survivor. *Jurnal Respirasi Unair.* 2022;8(1):15-25.



This work is licensed under a Creative Commons Attribution