Biomedical & Pharmacology Journal, March 2025. Vol. **18**(1), p. 739-748

Effectiveness and Adverse Drug Reaction Mechanisms Associated with Valproic Acid Use: A Cross-Sectional Prospective Study in Indonesia

Vitarani Dwi Ananda Ningrum[1]*, Irine Dyah Widyastuti[1], Rizaldy Taslim Pinzon[2], Rochmy Istikharah[1], Nashrul Hanif Al Hakim[1] and Naning Ni'mawati[1]

[1]Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Indonesia.
[2]Faculty of Medicine, Universitas Kristen Duta Wacana, Yogyakarta, Indonesia.
*Corresponding Author E-mail: vitarani.ningrum@uii.ac.id

https://dx.doi.org/10.13005/bpj/3124

(Received: 19 February 2025; accepted: 20 March 2025)

Valproic acid (VPA) is a broad-spectrum antiepileptic drug that can also be used to treat bipolar and other neurological disorders. Meanwhile, interindividual variability is known to significantly affect the clinical response to VPA use. This study aims to analyze the factors that affect the clinical response to VPA and prevalence of VPA adverse drug reactions (ADRs). An observational study with a prospective cross-sectional design was conducted by involving 87 outpatients from two private hospitals known for their excellence in neurology. The data on patients' demographic characteristics, the treatment received, clinical response to VPA, and adverse drug reactions (ADRs) were obtained from the medical records and patient interview. The clinical response to VPA was also confirmed by the patients' attending doctor, while the ADRs referred to the laboratory data on liver function and data from the medical records. A total of 84 patients (96.6%) receiving VPA showed the expected clinical response. There were no factors correlating with the effectiveness of VPA use ($p>0.05$). However, more than half of the patients experienced ADRs due to VPA use, including weight gain, hair loss, and hepatotoxicity. Although most of the patients have had their disorders controlled by VPA, an individualized approach is required to avoid the prevalence of ADRs, especially for patients with high-risk factors.

Keywords: Adverse drug reaction; Cross-Sectional; Effectiveness; Indonesia; Valproic acid.

Valproic acid (VPA) is an antiepileptic drug with a broad spectrum for various types of seizures. VPA works by inhibiting the gamma-aminobutyric acid transaminase (GABA-transaminase) enzyme and increasing the inhibitory activity of the GABA neurotransmitter in the brain. VPA also blocks sodium and calcium channels, thereby reducing excessive nerve excitation. [1,2] VPA can be used in the treatment of generalized, myoclonic, absence, and partial seizures. In addition, due to its relatively broad activity, VPA is used not only as a therapy for bipolar and some neurological disorders, such as migraine and neuropathic pain, but also as an adjunctive therapy in cancer. [3,4]

However, VPA shows high interindividual variability indicated by varied clinical responses in each patient. A study of 208 adult patients with epilepsy shows as high as 10-fold variability in VPA doses. [5] Several factors have proved to correlate with the clinical response to VPA use,

including gender, age, comorbidities, dose, dosage form, and duration of administration. [6–8]

In addition, VPA has a narrow therapeutic range (50-100 mcg/mL), which makes monitoring of VPA use becomes a crucial aspect. Various adverse drug reactions (ADRs), such as gastrointestinal disorders (nausea, vomiting, and diarrhea), tremor, and thrombocytopenia, frequently occur due to the accumulation of VPA concentration in the plasma. Other ADRs, such as hepatotoxicity, weight gain, and hair loss, are also frequently found during the use of VPA. [9]

Therefore, it is important to consider the strategies of VPA use based on the phenotypic and genotypic characteristics of the patient as well as the clinical conditions, dosage, and duration of use to guarantee the success of the treatment with minimal ADRs. However, research on the clinical response to VPA and ADRs of VPA remains limited to date. Therefore, this study aims to examine the factors that affect the effectiveness of VPA and the prevalence of its ADRs to allow such factors to be considered in the use of VPA in the health practice domain.

MATERIALS AND METHODS

This research was a prospective observational study with a cross-sectional design. Conducted from March 2022 to March 2023, this research involved the patients of Bethesda Hospital Yogyakarta and Bethesda Hospital Lempuyangwangi as hospitals with service excellence in the field of neurology. All the patients who received VPA and gave their consent were involved in the study. All subjects' names were recorded anonymously and only a patient code was given. Data can only be accessed by a research team approved by the hospital's ethics committee. The data was collected from the medical records, patient interviews, and the VPA clinical response confirmed by the doctor in charge.

The inclusion criteria of the study were patients with a minimum age of 18 years who received VPA therapy of at least one month per oral for various diagnoses. Meanwhile, pregnant or lactating women or patients with gastritis or chronic liver disorders as comorbidities were excluded from the study.

The data analysis used the chi-square test ($p<0.05$) in SPSS version 27 (IBM Corp, Armonk, NY, USA). The assessment of VPA effectiveness was based on whether the patient's illness was under control according to the doctor's assessment in the medical records. Meanwhile, the prevalence of ADRs comprised the incidence of hepatotoxicity based on the ALT level obtained from the laboratory data, hair loss, and weight gain, as well as other ADRs from the data experienced by the patients. Hepatotoxicity was defined as an ALT value greater than 50 U/L. The assessment of ADR causality used the Naranjo Algorithm, a tool also provided by the Indonesian Food and Drug Authority of the Republic of Indonesia in Bahasa.

RESULTS

A total of 87 patients met the inclusion criteria and were involved in the study. The patients' demographic characteristics and indications for VPA use based on the diagnoses are shown in Table 1.

Most of the patients were male adults with the three most diagnosed illnesses being stroke, epilepsy, and cephalgia. Based on Table 2, due to the actual count in the female group with

Table 1. Patients' characteristics

Characteristic	Total n (%)
Gender	
Male	45 (51.7)
Female	42 (48.3)
Age Category	
Adult (18-65 years)	59 (67.8)
Elderly (66-81 years)	28 (32.2)
Diagnosis	
Stroke	41 (47.1)
Epilepsy	18 (20.7)
Cephalgia	10 (11.5)
Vertigo	6 (6.9)
SOP*	4 (4.6)
Hydrocephalus	3 (3.4)
Migraine	2 (2.3)
Depression	2 (2.3)
SDH*	1 (1.5)

*SOP: space occupying process SDH: subdural hematoma

uncontrolled response was 0, so the subsequent analysis could not be done. Three patients (3.4%) were categorized as having ineffective therapy. Based on the age category, there was no significant correlation between age and clinical response (p=0.501). In addition, the results of the study showed that there was no significant correlation between diagnosis and clinical response to the use of VPA (p=0.062). Meanwhile, the dose of VPA for all the patients involved in this study was in the therapeutic range, with only 3.4% of them showing inappropriate clinical response.

Based on the potential drug interactions, there were 4 patients (4.6%) who had significant major drug interactions, but all of these patients showed the expected clinical response. The findings

Table 2. Correlation between the factors and VPA effectiveness

Category	Clinical Response n (%)		P value
	Controlled	Uncontrolled	
Gender*			-
Male	42 (48.3)	3 (3.4)	
Female	42 (48.3)	0 (0)	
Age (years)			0.501
18-65	58 (66.7)	1 (1.5)	
> 65-81	26 (29.9)	2 (2.3)	
Diagnosis			0.062
Stroke	39 (44.8)	2 (2.3)	
Epilepsy	18 (20.7)	0 (0)	
Vertigo	6 (6.9)	0 (0)	
Cephalgia	10 (11.5)	0 (0)	
Hydrocephalus	3 (3.4)	0 (0)	
Migraine	2 (2.3)	0 (0)	
SOP	4 (4.6)	0 (0)	
Depression	1 (1.5)	1 (1.5)	
SDH	1 (1.5)	0 (0)	
Dosage*			-
Appropriate	84 (96.6)	3 (3.4)	
Inappropriate	0 (0)	0 (0)	
Potential Major Drug Interactions*			-
No	80 (91.9)	3 (3.4)	
Yes	4 (4.6)	0 (0)	
Dosage form			0.696
Extended release	53 (60.9)	2 (2.3)	
Enteric coated	31 (35.6)	1 (1.5)	
Duration of administration (months)*			-
1 - <12	52 (59.8)	3 (3.4)	
12-36	17 (19.5)	0 (0)	
>36	15 (17.2)	0 (0)	

*Does not meet the criteria for performing a chi square test due to there being a cell with the actual count 0

Table 3. Prevalence of ADRs in VPA Use

Adverse Drug Reaction (ADR)	Total n (%)
Weight gain	27 (31.03)
Hair loss	14 (16.09)
Hepatotoxicity (ALT > 50 U/L)	9 (10.34)

of this study showed that the drug combinations frequently used were: 1) combination of VPA with levetiracetam and diazepam, 2) combination of VPA with phenytoin, phenobarbital, and diazepam, and 3) combination of VPA with betahistine mesylate. Meanwhile, based on the VPA dosage form, there was no significant correlation between extended-

release and enteric-coated dosage forms and the clinical response to VPA use (p = 0.696). The study results indicated that administering VPAs for over one month demonstrated good effectiveness in certain diagnoses. However, previous research reveals that the use of VPA for 1-2 years can provide better seizure control in epileptic patients although there is a risk of hepatotoxicity. The prevalence of VPA ADRs in this study is shown in Table 3. Of the total 87 patients, 50 (57.47%) experienced ADRs associated with the use of VPA. The ADRs found in this study included weight gain (27 patients), hair loss (14 patients), and hepatotoxicity (9 patients).

DISCUSSION

There has not been a study that specifically examines the effectiveness and adverse drug reactions (ADRs) of VPA in the Indonesian population. Since VPA could be prescribed for a range of clinical diagnoses according to guidelines and used for a long period, understanding its effectiveness profile and the prevalence of ADRs is essential to fully describe the clinical response and its safety.

As stated in Table 1, VPA could be prescribed for a variety of indications. Several studies suggest that valproic acid can protect brain cells from further damage caused by brain injury. This is because valproic acid works by modulating neurotransmitter pathways in the brain, including GABA (gamma-aminobutyric acid), and it can affect the repairs to inflammation and oxidative stress. [10–13]

Meanwhile, this study found no factors correlated with the therapeutic effectiveness of VPA use. Similar studies show no correlation between gender and clinical response to VPA use. [6–8] In contrast, there is a study which finds that women have a higher level of VPA compared

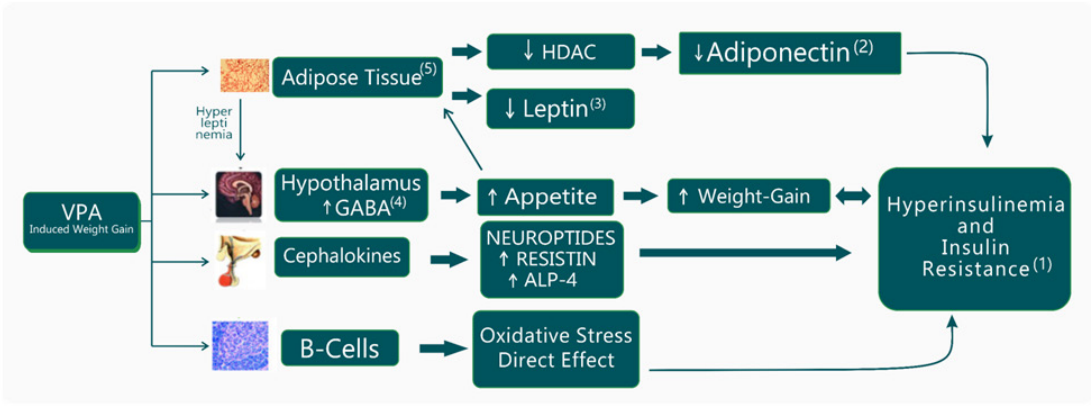

Fig. 1. Mechanism of VPA Inducing Body Weight Increase

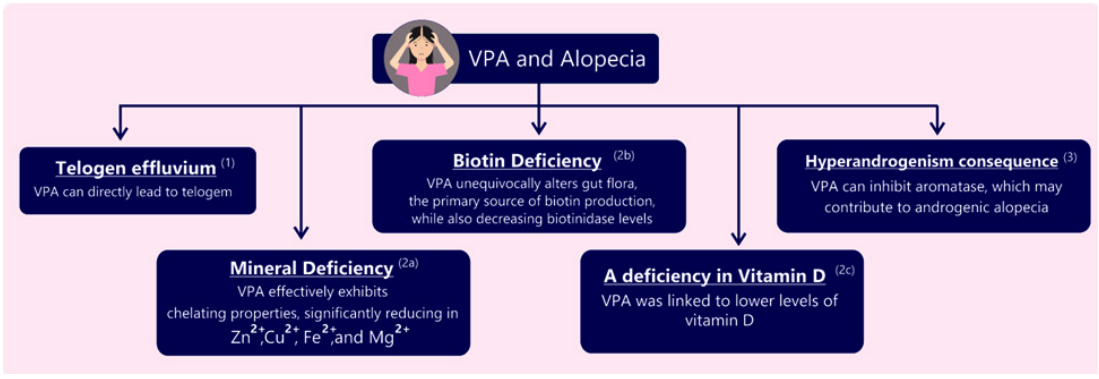

Fig. 2. Mechanism of VPA Inducing Hair Loss

to men for the same administered dose, which is likely associated with hormonal differences and effects in women. Another study also suggests that women tend to have a slower metabolism, thus causing VPA levels to be higher in women. [14] It is suggested that VPA tends to be more effective in women compared to men at a similar dose. In addition, the International League Against Epilepsy (ILAE) states that women tend to be more sensitive to adverse drug reactions and require lower doses to achieve optimal control of seizures. [15] The limited number of patients participating in this study, including the proportion of women who experienced uncontrolled illnesses, and the plasma concentration of VPA being unanalyzed in this study have become the reasons for the absence of in-depth investigation.

Table 2. showed that age was not the covariate correlated with the effectiveness of VPAs. Most studies analyze safety risks, instead of clinical responses. It may be assumed that in the clinical setting, there is no difference in effectiveness between the age categories of patients. Young adult patients show good tolerability towards the use of VPA although they remain susceptible to some of the ADRs. Meanwhile, older adult and elderly patients are more susceptible to ADRs due to their slow metabolism, thus requiring more strict monitoring. [16–18]

In addition, Table 2. showed that the administration of appropriate doses of VPA resulted in symptoms and disease control in most patients as expected. Administering a high dose of valproic acid (>1000mg/day) to epileptic patients can improve seizure control, but a higher dose may increase the risk of ADRs. [19] Previous research shows that VPA with the extended-release dosage form has an advantage in terms of tolerability, with fewer ADRs on the gastrointestinal tract compared to the immediate-release dosage form. However, both forms have similar seizure control. [20] Meanwhile, another study shows that the enteric-coated dosage form has an advantage in reducing gastric irritation compared to other dosage forms. However, the effectiveness in controlling seizures is as good as the extended-release and immediate-release dosage forms. [21] The results of those studies were confirmed by this research finding that there

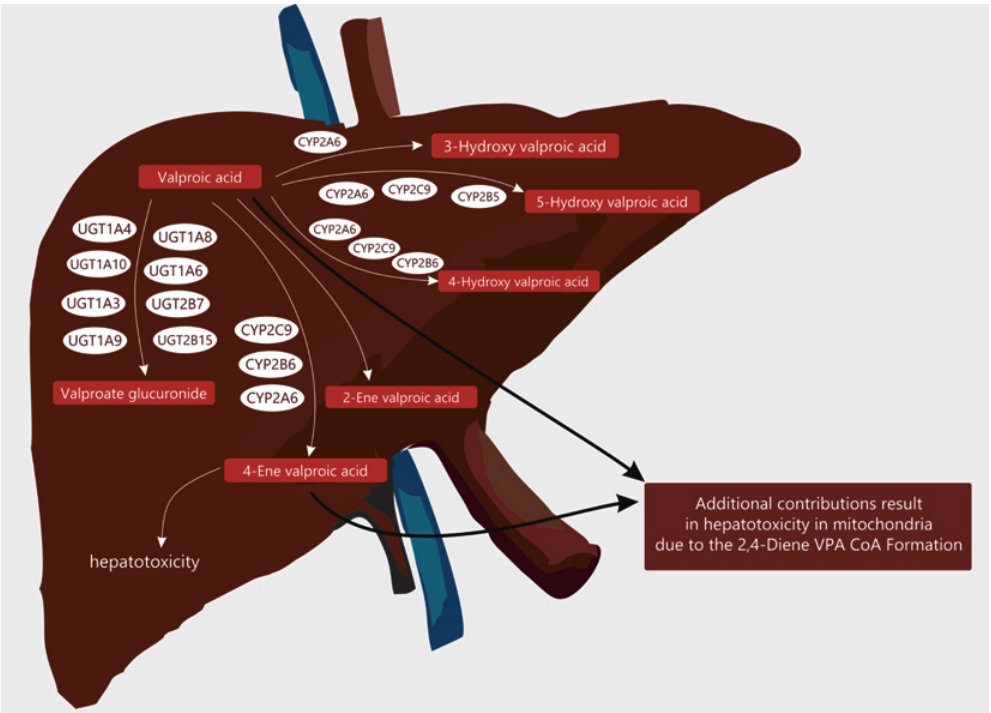

Fig. 3. Hepatotoxicity due to VPA

The genes encoding liver metabolic proteins can vary functionally due to genetic variation

were no ADR associated with gastrointestinal discomfort caused by all patients prescribed VPA in the extended-release or enteric-coated dosage form.

This study involved patients who consumed VPA for at least 1 month. Some patients have even been given VPAs as children. The use of VPAs over a chronic period is sometimes associated with more serious effects. A study reveals that long-term use of VPA is associated with cognitive decline in patients, especially those with chronic high doses. [22] Other studies show that long-term use of VPA is associated with an increased risk of osteoporosis and fractures in some patients. [23–25]. No ADRs were found to be related to cognitive or bone disorders and fractures in this study, as shown in Table 3.

Related to these findings, weight gain is the most common ADR found in the use of VPA. The mechanism in inducing weight gain is likely through: 1) insulin resistance which can increase appetite and body fat accumulation, 2) decreased adiponectin levels which are associated with a deterioration in the metabolic regulation of the body especially for glucose and fat, 3) decreased leptin (a hormone that controls satiety), 4) neurotransmitter changes in the hypothalamus due to the influence of VPA on appetite regulation through GABAergic interactions, and 5) direct effect on adipose tissue which leads to decreased fat burning and increased fat storage. This ADR mechanism is as in Figure 1. [26,27]

This type of ADR tends to be beneficial for thin patients because a randomized control trial (RCT) on healthy volunteers shows a decrease in blood glucose, resulting in increased appetite in the group receiving VPA. [28] However, there are concerns about insulin resistance and other secondary metabolic abnormalities. Therefore, gaining more than 2 kg of weight after 1 month of VPA use still needs vigilance since it is necessary to replace therapy in certain conditions. [29] Genetic factors are known to influence both the effectiveness of valproate (VPA) and the occurrence of adverse drug reactions (ADRs), including weight gain. A study conducted on the Indonesian population using VPA found that over 30% of patients experienced weight gain. This prevalence may vary among different racial groups, as a recent study indicated a significant correlation between the rs1137101 variant of the LEPR gene (a metabolic regulator) and the risk of weight gain. [30]

Meanwhile, 14 patients experienced hair loss due to the use of VPA. Previous studies find that VPA induces such condition because it triggers telogen effluvium (1), in which hair follicles enter the resting phase of hair growth earlier. This leads to hair loss without scars on the scalp. [31] VPA can also cause a decrease in the zinc, (2a) biotin (2b), and vitamin D (2c) levels in the body, which play an important role in hair follicle cell division and keratin metabolism in hair. [32,33] In addition to that, androgenic hormones also play a role in this condition (3). The risk of hair loss associated with the use of VPA is influenced by genetic factors, similar to weight gain. For instance, the rs1137101 polymorphism in the LEPR gene is linked to an increased frequency of hair loss. In contrast, the rs4480 variant of the SOD2 gene, which encodes a mitochondrial scavenging enzyme, appears to offer a protective effect against hair loss. [30] However, hair loss due to the use of VPA is reversible and will return to normal when the dose is lowered or the use is stopped. [34] This ADR mechanism is illustrated in Figure 2. [31–34]

A total of 9 patients experienced an ADR in the form of hepatotoxicity, which was characterized by the increased ALT levels. The mean ALT value in these patients was 63.13±17.93 U/L. Although AST is also an enzyme marker of liver damage, its sensitivity is lower than that of ALT because AST is also a marker of cardiotoxicity. [35,36] Hepatotoxicity can occur in the use of VPA because the metabolite, 2-propyl-4-pentenoic acid**,** inhibits the beta-oxidation of fats in the mitochondria, which results in the accumulation of lipids in the liver. In addition, the toxic metabolite of VPA can damage hepatocytes through decreased glutathione and antioxidant storage which results in oxidative stress and disruption of cell membrane structure, induce fatty liver through inhibition of carnitine palmitoyltransferase I, increase nuclear receptor, peroxisome proliferator-activated receptor-gamma, and acyl-CoA thioesterase 1, as well as induce long-chain fatty acid uptake and triglyceride synthesis. Some cases of hepatotoxicity are caused by idiosyncratic reactions involving neurological

mechanisms. [37–40] This mechanism and the protein enzymes involved in VPA metabolism shown in Figure 3. [40,41]

VPA administration can also aggravate liver damage, especially in patients with metabolic syndrome. Incidence of ADR associated with VPA use in the form of hepatotoxicity can even become fatal, affecting 20% of the research subjects. [37] Compared to the two types of adverse drug reactions (ADRs) associated with the previous use of valproic acid (VPA), hepatotoxicity represents the most serious form of ADR. It can lead to patients needing to discontinue medication or need treatment for liver damage or necessitate a change in therapy. Consequently, there is more pharmacogenetic research focused on hepatotoxicity related to VPA than on ADRs from other medications. At least six gene variants have been identified that increase the risk of hepatotoxicity. These include CPS1 (4217C>A), GLUL (rs107997771), POLG (p.Q1236H; p.E1143G), GST (GSTM1-GSTTI-), SOD2 (Val16Ala), and variants in CYP2C9 (rs1057910). These genetic factors have been associated with elevated levels of ammonia, GGT, ALT, or VPA in the blood, indicating a higher risk for hepatotoxicity. [30,42]

This study is the first to reveal the prevalence of adverse drug reactions (ADRs) associated with the use of valproic acid (VPA) for various indications in the Indonesian population, a topic that has not been explored previously. Overall, VPAs are considered effective and safe for patients in Indonesia based on the clinical improvement and prevalence of ADRs observed in this study. Most adverse drug reactions (ADRs) reported are weight gain and hair loss, which patients can often tolerate. However, the most severe ADR, hepatotoxicity, occurs with an incidence of less than 10%. This highlights the need for proper management to prevent further complications.

The findings of this study regarding the incidence of adverse drug reactions (ADRs) need to be further investigated to identify genetic factors that contribute to the risk of ADR events in the Indonesian population. While this study focuses solely on Indonesians, previous research has shown that Indonesia's genetic profile is similar to that of Indian and Chinese populations. Therefore, additional studies are necessary to confirm these earlier findings, particularly concerning the safe therapeutic use of valproic acid (VPA).

This study has some limitations in terms of the research location that was non-randomly selected and the variation in the diagnosis of the participating patients, which make generalization of the findings require further studies. Although various efforts have been made to obtain an adequate number of patients by involving hospitals with excellence in neurology, this study has not been able to reveal the risk factors for ADRs caused by VPA use. In addition, collecting data at a single point in time limits our ability to establish a clear temporal relationship between VPA use and its adverse drug reactions (ADRs). Therefore, longitudinal studies with an analysis of the risk factors that contribute to the incidence of ADRs in VPA use associated with patients' phenotypic and genotypical aspects should be conducted to provide more effective strategies for the use of VPA, especially with minimal ADRs.

CONCLUSION

The top three indications of VPA use include stroke, epilepsy, and cephalgia. Almost all patients showed a positive clinical response to the use of VPA. There were no factors associated with the effectiveness of VPA for various diagnoses ($p>0.05$). However, the prevalence of ADRs associated with VPA includes weight gain, hair loss, and hepatotoxicity. Considering that the prevalence of hepatotoxicity related to VPA has reached 10%, we recommend that healthcare professionals take proactive measures in monitoring and addressing this concern.

ACKNOWLEDGMENTS

The authors would like to thank the management of Bethesda Hospital for facilitating the location of this study.

Funding source

Research Grant No. 002/Dir/DPPM/70/Pen.Unggulan/XI from Directorate of Research and Community Services of Universitas Islam Indonesia

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This study has received approval from the Health Research Ethics Committee of Bethesda Hospital Yogyakarta (No. 31/KEPK-RSB/II/22).

Informed Consent Statement

All participants were enrolled following written informed consent.

Clinical Trial Registration

This research does not involve any clinical trials

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Not Applicable.

Author's Contribution

Vitarani Dwi Ananda Ningrum: Conceptualization, Methodology, Analysis, Writing – Original Draft; Irine Dyah Widyastuti: Supervision, Data Collection, Analysis; Rizaldy Taslim Pinzon: Visualization, Data Collection, Supervision; Rochmy Istikharah: Conceptualization, Methodology, Funding Acquisition; Nashrul Hanif Al Hakim: Data Collection, Analysis, Project Administration; Naning Ni'mawati: Analysis, Resources, Writing – Original Draft

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