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Research Article

Therapeutic Effects of Methylprednisolone on Clinical Symptoms in COVID-19 Patients at Dr. R. Goeteng Taroenadibrata Hospital

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Abstract
COVID-19 is a respiratory syndrome disease in humans caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Until now, treatment for COVID-19 has not been found. This study aimed to observed a therapeutic effect of methylprednisolone in COVID-19 patients. Medical records of COVID-19 patients at Dr. R. Goeteng Taroenadibrata Purbalingga Hospital were collected retrospectively as part of this descriptive observational study from October 2020 to September 2021. Utilizing the Wilcoxon and Sign Test, a statistical analysis was conducted to determine the therapeutic effect of methylprednisolone on variables such as temperature, respiratory rate, oxygen saturation, cough, and shortness of breath. A total of 132 patients met the inclusion criteria, with 87 patients in mild severity, 22 patients with moderate severity, and 23 patients with severe severity. The clinical symptoms of cough, dyspnea, RR values, and SpO_2 improved when methylprednisolone was given to mild COVID-19 patients receiving treatment at RSUD Dr. R. Goeteng Taroenadibrata Purbalingga. Additionally, clinical symptoms related to cough, SpO_2, and temperature parameters improved in patients with moderate severity; in contrast, breathlessness, respiratory distress, SpO_2, and temperature parameters improved in patients with severe severity. In conclusion, Goeteng Taroenadibrata Hospital COVID-19 patients report improved clinical symptoms when receiving methylprednisolone.

Keywords: clinical symptoms, corticosteroids, COVID-19, methylprednisolone

Efek Terapeutik Penggunaan Metilprednisolon terhadap Gejala Klinis pada Pasien COVID-19 Rawat Inap di RSUD Dr. R. Goeteng Taroenadibrata

Abstrak
Coronavirus disease (COVID-19) adalah penyakit sindrom pernapasan pada manusia yang disebabkan oleh *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). Hingga saat ini, pengobatan COVID-19 yang efektif belum ditemukan. Penelitian ini dilakukan untuk mengetahui apakah terdapat efek terapeutik penggunaan metilprednisolon pada pasien COVID-19. Penelitian ini bersifat deskriptif observasional dengan metode pengambilan data secara retrospektif yang dilakukan dengan mengambil data rekam medis pasien COVID-19 rawat inap di RSUD Dr. R. Goeteng Taroenadibrata Purbalingga periode Oktober 2020–September 2021. Pengambilan data dilakukan dengan total sampling menggunakan uji Wilcoxon dan Sign Test digunakan untuk melihat efek terapeutik metilprednisolon terhadap parameter suhu, RR, SpO_2, batuk, dan sesak pada pasien COVID-19. Sebanyak 132 pasien memenuhi kriteria inklusi dengan rincian 87 pasien dengan tingkat keparahan ringan, 22 pasien dengan tingkat keparahan sedang, dan 23 pasien dengan tingkat keparahan berat. Pemberian metilprednisolon pada pasien COVID-19 dengan keparahan ringan menghasilkan perbaikan gejala klinis batuk, sesak, nilai RR, dan SpO_2. Selain itu, pasien dengan tingkat keparahan sedang menunjukkan perbaikan gejala klinis terkait parameter batuk, SpO_2, dan suhu; sebaliknya, pasien dengan tingkat keparahan yang parah menunjukkan perbaikan gejala klinis terkait sesak napas, RR, SpO_2, dan parameter suhu. Kesimpulannya, terdapat perbaikan gejala klinis pada pasien COVID-19 di RS Goeteng Taroenadibrata yang mendapatkan metilprednisolon.

Kata kunci: COVID-19, gejala klinis, kortikosteroid, metilprednisolon

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Introduction

Coronavirus disease is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the genus betacoronavirus.[1] The spread of this virus is increasing, so that on March 11, 2020, WHO declared COVID-19 a global pandemic emergency. As of April 2023, there were 762 million confirmed cases of COVID-19 in the world with a death toll of 6.8 million people. In Indonesia, it is reported that up to April 2023, there have been 6.7 million confirmed cases with a death toll of 161,000 people.[2]

The condition of COVID-19 patients with severe and critical severity is characterized by an increase in cytokine storms. This cytokine storm causes systemic inflammation which results in organ function failure. Until now, there has been no effective therapy for COVID-19. Clinical research has proven that some clinical manifestations of severe pneumonia, such as high fever, shortness of breath, decreased oxygen saturation, progressive pneumonitis, various severe complications, and even the risk of death, are all related to inflammatory factors. Corticosteroid drugs can be used as drugs to treat inflammation caused by cytokine storms.[3] Corticosteroids act on almost all cell types and especially on immune cells where they have been shown to have potent immunosuppressive and anti-inflammatory activity.[4]

One example of a corticosteroid that is often used is methylprednisolone. In the COVID-19 therapy guide in Indonesia prepared by PDPI, PERKI, PAPDI, and PERDATIN (2020), methylprednisolone is indicated for COVID-19 patients with moderate, severe and critical severity.[5] Since the publication of this treatment, there have been many developments related to COVID-19 therapy, including the use of methylprednisolone. The use of methylprednisolone was previously stated in PDPI, PERKI, PAPDI, and PERDATIN (2020) as indicated for patients with the moderate, severe, and critical diseases. Then, after the publication of the COVID-19 Drug Information Guideline in Indonesia and the latest COVID-19 Management Protocol by PDPI, PERKI, PAPDI, and PERDATIN (2022), methylprednisolone can only be used in severe or critical COVID-19 cases.[6]

Methylprednisolone is used to treat severe acute respiratory infections of viral etiology due to its anti-inflammatory effects. However, the use of methylprednisolone in patients with severe COVID-19 remains controversial.[7] According to research by Zanella *et al*. (2021), methylprednisolone is used for anti-inflammatory therapy to combat excessive and uncontrolled release of pro-inflammatory cytokines, by paying attention to the appropriate administration time according to different individual indicators.[8] Therefore, the use of methylprednisolone must be tailored to each patient to achieve maximum therapeutic effect. Early use of methylprednisolone not only reduces the risk of critical disease progression for patients with severe COVID-19 but can also reduce mortality, demonstrating the effectiveness and safety of using low and moderate doses of methylprednisolone.[7]

Cytokine storm syndrome has been leading to overwhelming systemic inflammation and multiorgan failure with high mortality. Corticosteroid (including methylprednisolone) administration may benefit through the impairment of cytokine storm occurrence and leukocyte lung infiltration, which decreases tissue fibrosis and alveolar fluid accumulation. Research regarding the effect of using methylprednisolone on COVID-19 patients and similar research in Indonesia is still limited. Therefore, it is necessary to carry

out further research regarding the therapeutic effects of using methylprednisolone for COVID-19 therapy. Hospitalized COVID-19 patients may benefit from therapy based on the research findings.

Method

This observational study was carried out at the COVID-19 referral Dr. R. Goeteng Taroenadibrata Purbalingga Hospital. The research subjects were patients with confirmed COVID-19 and was taken retrospectively for the period October 2020–September 2021 using a total sampling technique. The instrument used in this research was medical record data from COVID-19 patients.

The sample was determined by research subjects who met the inclusion criteria, that are inpatients with confirmed COVID-19 aged ≥18 years who had used methylprednisolone for at least 72 hours with complete medical record data (including comorbid condition). And the exclusion criteria are as follows: individuals with specific situations, such as expectant mothers, patients who passed away while using methylprednisolone, patients receiving therapy that combines corticosteroids. The independent variable of this study was the use of methylprednisolone in patients. Meanwhile, the dependent variable in this study is the clinical symptoms of COVID-19 after the patient received methylprednisolone therapy such as respiratory rate (RR) values, SpO_2, temperature, cough symptoms, and shortness of breath. Data analysis was carried out regarding the effect of therapy before and after the use of methylprednisolone on the patient's clinical symptoms statistically using the Wilcoxon test and sign test. This research has received an appropriate ethical review from the Health Research Ethics Commission, Faculty of Health Sciences, Jenderal Soedirman University with number 682/EC/KEPK/III/2022.

Result

The number of samples that met the inclusion criteria was 132 patients, consisting of 87 patients with mild severity, 22 patients with moderate severity, and 23 patients with severe severity. Based on the research results, there were 87 patients (65.91%), 51 patients (51%) female and 49 patients (49%) male with mild severity, 22 patients (16.67%) with moderate severity, and 23 patients (17.42%) with severe severity (Table 1). Many as 80% of patients infected with COVID-19 are of mild severity.[9,10,11,13]

It was found that 68 patients (51.52%) were male and 64 patients (48.48%) were female. In the study, the results showed that 14 patients (10.61%) were in late adolescence (18–25 years), 18 patients (13.64%) were in early adulthood (26–35 years), 19 patients (14.39%) were in late adulthood (36–45 years), 37 patients (28.03%) were early elderly (46–55 years), 27 patients (20.45%) were late elderly (56-65 years), and 17 patients (12.88%) were elderly (>65 years) (Table 2).

Table 1 Characteristics of Patient Disease Severity in Hospitalized COVID-19 Patients

No.	Disease Severity Level	Amount	Percentage (%)
1	Mild	87	65,91
2	Moderate	22	16,67
3	Severe	23	17,42
	Total	132	100,00

Table 2 Gender and Age Characteristics in Hospitalized COVID-19 Patients

No.	Characteristics	Severity Level			Total N=132
		Mild N=87 (%)	Moderate N=22 (%)	Severe N=23 (%)	
1	**Gender**				
	Male	42 (48.28)	15 (68.18)	11 (47.83)	68 (51.52)
	Female	45 (51.72)	7 (31.82)	12 (52.17)	64 (48.48)
2	**Age**				
	18–25 years	14 (16.09)	0 (0.00)	0 (0.00)	14 (10.61)
	26–35 years	12 (13.79)	3 (13.64)	3 (13.04)	18 (13.64)
	36–45 years	9 (10.34)	8 (36.36)	2 (8.70)	19 (14.39)
	46–55 years	24 (27.59)	5 (22.73)	8 (34.78)	37 (28.03)
	56–65 years	16 (18.39)	4 (18.18)	7 (30.43)	27 (20.45)
	>65 years	12 (13.79)	2 (9.09)	3 (13.04)	17 (12.88)

The symptoms most commonly experienced by COVID-19 patients included coughing in 78 patients (59.09%), shortness of breath in 73 patients (55.30%), and fever in 21 patients (15.91%). The most common comorbidities in COVID-19 patients at Goeteng Taroenadibrata Regional Hospital were hypertension with 23 cases (17.42%), pneumonia with 23 cases (17.42%), congestive heart failure (CHF) with 16 cases (12.12%), and asthma with 10 cases (7.58%) (Table 3).

As shown in Table 4, inpatients hospitalized with COVID-19 were given methylprednisolone at varying doses. The dose and route of administration of methylprednisolone were most commonly used intravenously with a dose of 3x62.5 mg, namely a total of 55 patients (41.67%). The duration of administration of methylprednisolone which is most commonly used in hospitalized COVID-19 patients is 6-7 days (Table 5). There was a therapeutic effect of using methylprednisolone on clinical symptoms of cough parameters, SpO_2, and temperature (p= <0.01; 0.01; <0.01 respectively) in patients with moderate severity, and there was an effect therapy using methylprednisolone on clinical symptoms in the parameters of shortness of breath, RR, SpO_2, and temperature (p= <0.01; 0.01; <0.01; <0.01 respectively) in patients with severe severity (Table 6 and 7). The results showed that 43 patients experienced improvement in cough symptoms, 31 patients still had a cough, and 8 patients experienced worsening cough symptoms. The results of statistical tests using the sign test for shortness of breath parameters showed that 40 patients experienced improvement in shortness of breath symptoms, 33 patients still had shortness of breath, and 4 patients experienced worsening shortness of breath symptoms.

Discussion

COVID-19 patients with moderate, severe, and critical conditions were previously treated with methylprednisolone as prescribed. There is currently no known cure for COVID-19. Present this study evaluate a therapeutic effect on the use of methylprednisolone in COVID-19 patients with various characteristic and comorbidities. Based on the result the

Table 3 Characteristics of Symptoms and Comorbids in Hospitalized COVID-19 Patients

No.	Characteristics	Severity Level			Total
		Mild	Moderate	Severe	
1	**Symptoms***				
	Fever	17 (12.88)	1 (0.76)	3 (2.27)	21 (15.91)
	Shortness of breath	39 (29.55)	3 (9.85)	21 (15.91)	73 (55.30)
	Cough	44 (33.33)	17 (12.88)	17 (12.88)	78 (59.09)
2	**Comorbids****				
	Hypertensiom	12 (9.09)	6 (4.55)	5 (3.79)	23 (17.42)
	Pneumonia	15 (11.36)	3 (2.27)	5 (3.79)	23 (17.42)
	CHF	8 (6.06)	4 (3.03)	4 (3.03)	16 (12.12)
	Asthma	2 (1.52)	2 (1.52)	6 (4.55)	10 (7.58)
	Diabetes mellitus	8 (6.06)	0 (0.00)	0 (0.00)	8 (6.06)
	Pulmonary TB	2 (1.52)	1 (0.76)	0 (0.00)	3 (2.27)
	COPD	0 (0.00)	2 (1.52)	0 (0.00)	2 (1.52)
	CKD	1 (0.76)	0 (0.00)	0 (0.00)	1 (0.76)
	Others	15 (11.36)	4 (3.03)	3 (2.27)	22 (16.67)

Information:
*: Patients can have more than 1 symptom
**: Patients can have more than 1 comorbidity
CHF (congestive heart failure); CKD (chronic kidney disease); TB (tuberculosis); COPD (chronic obstructive pulmonary disease)
Others: kidney failure, dyspepsia, pharyngitis, gastritis, GERD (gastroesophageal reflux disease), hematuria, cholesterol

predominance of male COVID-19 patients is probably because men usually leave the house more to do work. Apart from that, more men are active smokers. The high number of cases in male patients is influenced by factors such as ACE2 receptors which are higher in men than women. The tendency of men to smoke increases ACE2 receptors due to the nicotine content in cigarettes. Increased ACE2 receptors facilitate the attachment of SARS-CoV-2 to adhere to cell surfaces making them susceptible to infection with COVID-19.[13] The majority of COVID-19 patients are over 50 years old, possibly because the immune system declines with age. The adaptive immune system also influences the body's immunity in fighting COVID-19 infection in patients with comorbid conditions and the elderly.[14] The symptoms of COVID-19 that often appear in the form of coughing are caused by the COVID-19 virus attaching to host cells that can express the angiotensin-converting enzyme (ACE2) receptor, which is abundant in the upper respiratory tract and stimulates mucus production so that COVID-19 patients tend to have cough symptoms.[15] Hypertension can worsen the condition of patients infected with COVID-19, this virus will bind to angiotensin-converting enzyme 2 (ACE2), which is an enzyme that attaches to the outer surface of several organs in the body, after binding to this enzyme, the virus can enter the organ and cause the patient to become infected with COVID-19.[16]

There are no established guidelines for COVID-19 and we rely on the previous treatments for SARS, MERS or influenza or on expert opinions.[17] Many of the drugs currently effective in COVID disease appear to have links to the NF-κB cascade of immune regulation. Dexamethasone is among the

Table 4 Methylprednisolone Dosage, Frequency, and Route of Administration in Hospitalized COVID-19 Patients

No	Characteristics		Severity Level			Total N=132
			Mild N=87 (%)	Moderate N=22 (%)	Severe N=23 (%)	
1	PO	1 x 6	2 (2.30)	0 (0.00)	0 (0.00)	2 (1.52)
		1 x 8	0 (0.00)	2 (9.09)	0 (0.00)	2 (1.52)
		2 x 8	2 (2.30)	2 (9.09)	0 (0.00)	4 (3.03)
		3 x 4	3 (3.45)	0 (0.00)	0 (0.00)	3 (2.27)
		3 x 6	18 (20.69)	8 (36.36)	0 (0.00)	26 (19.70)
		3 x 8	3 (3.45)	1 (4.55)	2 (8.70)	6 (4.55)
		Total	28 (32.18)	13 (59.09)	2 (8.70)	43 (32.58)
2	IV	1 x 62.5	5 (5.75)	1 (4.55)	0 (0.00)	6 (4.5)
		2 x 62.5	13 (14.94)	6 (27.27)	9 (39.13)	28 (21.21)
		3 x 62.5	41 (47.13)	2 (9.09)	12 (52.17)	55 (41.67)
		Total	59 (67.82)	9 (40.91)	21 (91.30)	89 (67.42)

two glucocorticoids (prednisolone being the other) which has the inhibitory action on the NF-κB pathway. Glucocorticoids increase expression of IκB, which helps retain NF-κB within the cellular cytoplasm. The beneficial role of dexamethasone may be at least partly related to the inhibition of NF-κB activation in the severe-critically ill COVID-19 patients. The role of steroids generally in COVID-19 is by inhibiting the action and expression of many molecules involved in pneumonia associated inflammatory response. However, this glucocorticoid is associated with immunosuppression, augmented blood pressure, and glycemia as major side effects.[18]

The data from some clinical trial suggests that the role of corticosteroid treatment in SARS-CoV-2 virus infection should be reconsidered as a valuable option. Given the pathophysiology of the disease, corticosteroids could have beneficial effects on both hyperinflammation and acute respiratory distress syndrome (ARDS) as COVID-19 seems to be a steroid responsive disease. In the same time, this anti-inflammatory and immunomodulatory treatment is easily accessible, has proven benefits, and the associated costs are quite low. When administering corticosteroid therapy, the risk-benefit ratio of this type of treatment must be considered, depending on each patient.[19]

In a study of the 1,128 interventions conducted by tele pharmacy teams, 743

Table 5 Duration of Use Methylprednisolone in Hospitalized COVID-19 Patients

No.	Duration of Use	Severity Level			Total N=132
		Mild N=87 (%)	Moderate N=22 (%)	Severe N=23 (%)	
1	3–5 days	26 (29.89)	8 (36.36)	10 (43.38)	44 (33.33)
2	6–7 days	33 (37.93)	6 (27.27)	6 (26.09)	45 (34.09)
3	>7 days	28 (32.18)	8 (36.36)	7 (30.43)	43 (32.58)

Table 6 Differences in Clinical Symptoms of Cough and Shortness Before and After Administration of Methylprednisolone in Hospitalized COVID-19 Patients

No.	Symptom (Before – After Use)	Severity Level			Total N=132
		Mild N=87 (%)	Moderate N=22 (%)	Severe N=23 (%)	
1	**Cough**				
	No cough – no cough[a]	40 (45.98)	5 (22.73)	5 (21.74)	50 (37.88)
	Cough – cough[a]	14 (16.09)	7 (31.82)	10 (43.48)	31 (23.48)
	No cough – cough[b]	5 (5.75)	0 (0.00)	3 (13.04)	8 (6.06)
	Cough – no cough[c]	28 (32.18)	10 (45.45)	5 (21.74)	43 (32.58)
	p-value	<0.01*	<0.01*	0.72	
2	**Shortness of Breath**				
	No – No[a]	45 (51.72)	8 (36.36)	2 (8.70)	55 (41.67)
	Yes – Yes[a]	13 (14.94)	7 (31.82)	13 (56.52)	33 (25.00)
	No – Yes[b]	3 (3.45)	1 (4.55)	0 (0.00)	4 (3.03)
	Yes – No[c]	26 (29.89)	6 (27.27)	8 (34.78)	40 (30.30)
	p-value	0.08	0.12	<0.01*	

Information:
*: p-value < 0,05 indicated there is a significant difference between before and after the use of methylprednisolone.
[a]: There was no improvement or worsening of symptoms
[b]: There was worsening of symptoms
[c]: There was improvement of symptoms

(65.86%) were drug-related. The top five drugs affected by pharmacist interventions were hydroxychloroquine (14.93%), azithromycin (13.99%), paracetamol 12.51%, corticosteroid (9.95%), and long-acting beta agonist (6.86%).[20]

Indication for using corticosteroids should be based on an a priori risk-benefit analysis. Dexamethasone 6 mg once daily or equivalents (prednisone 40 mg, methylprednisolone 32 mg, hydrocortisone 160 mg) is the daily dosage recommended. Hydrocortisone having the shorter half-life should be used in patients with SARS-CoV-2 and sepsis. Corticosteroids are recommended in patients with severe SARS-CoV-2 infection requiring high-flow oxygen and/or mechanical ventilation and as an alternative to remdesivir in patients with hypoxemia not requiring high oxygen flows. In patients with non-severe SARS-CoV-2 infection corticosteroids use should rather be restrictive, and not recommended in patients without hypoxemia or with no need for hospitalization. A short course ≤7 days being indicated.[19]

Methylprednisolone is used to treat severe acute respiratory infections of viral etiology due to its anti-inflammatory effects. However, the use of methylprednisolone in patients with severe COVID-19 remains controversia.[17] The maximum dosage of methylprednisolone tablets is 32 mg per day, and the maximum dosage of lyophilized injection powder is 500 mg per day.[21] Methylprednisolone may be administered for a maximum of 10 days, or until the patient returns home following therapy.[6]

Coughing is one of clinical symptoms in COVID-19 patients. Coughing is a defense mechanism to clear the airways when the mucociliary is ineffective due to increased mucus secretion, inflammation, infection, or ciliary dysfunction. Methylprednisolone is

Table 7 Differences in Clinical Symptoms in RR, SpO_2, and Temperature Parameters in Hospitalized COVID-19

No	Severity of Symptoms	Parameters	Mean±SD		p-value
			pre	post	
1	Mild	RR	20.62±2.51	20.29±3.22	0.05*
		SpO_2	97.82±1.32	97.13±1.99	<0.01*
		Temperature	36.28±0.45	36±0	0.95
2	Moderate	RR	21.09±3.25	20.54±5.20	0.27
		SpO_2	94.63±1.25	96.59±2.85	0.01*
		Temperature	35.33±1.15	36±0	<0.01*
3	Severe	RR	24.13±3.89	21.39±4.01	0.01*
		SpO_2	86.17±10.73	93.26±6.46	<0.01*
		Temperature	36±0	36.16±0.40	<0.01*

Information:
*: p-value < 0.05 indicated there is a significant difference between before and after the use of methylprednisolone

a steroid that can affect coughing because it has an effect as a mucoregulator which works by regulating mucus secretion, inflammation, and infection. However, in this study, methylprednisolone did not provide clinical improvement in cough parameters for patients with severe severity. This is because coughing is a clinical sign that has the longest duration after therapy.[22] Methylprednisolone is a steroid that affects shortness of breath through an anti-inflammatory effect on the airways by reducing the number of inflammatory cells in the airways. This effect is achieved by inhibiting the recruitment of inflammatory cells into the airways by suppressing the production of chemotactic mediators.[22]

The person in an older age group may have multiple comorbidities by aging process such as atherosclerosis, hypertension, diabetes mellitus, metabolic syndrome and chronic kidney disease and they might have pre-existing subclinical or subtle inflammations. Therefore, if they are infected by COVID-19, there is high possibility that they will progress to severe "cytokine storm".[17]

Our limitation study is that the corticosteroid methylprednisolone to aid COVID-19 patients overcome their clinical symptoms is administered in combination with other medications such as oxygen, symptomatic medications, and antivirals. Another limitation is that the relatively small number of samples, especially in patients with severe severity, can be a limitation of the research which means that when statistical analysis is carried out, it is not possible to clearly determine the therapeutic effect of using methylprednisolone on severe severity. Therefore, it is hoped that this research would serve as information for upgrading the most recent COVID-19 treatment per Minister of Health regulations. Research indicates that in order to improve the accuracy of therapy effects, pharmacist have to monitor patient, supporting examinations and periodic medical record data recording are required. This research may be taken into account when updating COVID-19 treatment protocols in accordance with Minister of Health regulations.

Conclusion

The administration of methylprednisolone to severe COVID-19 patients hospitalized at RSUD. Dr. R. Goeteng Taroenadibrata Purbalingga resulted in improvements in the clinical symptoms of cough, shortness, RR, and SpO_2 values. Additionally, patients with moderate severity showed improvements in their clinical symptoms related to cough, SpO_2, and temperature parameters; in contrast, patients with severe severity showed improvements in their clinical symptoms related to shortness of breath, RR, SpO_2, and temperature parameters.

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Conflict of Interest

All authors declare that there is no potential conflict of interest with the research, authorship, and/or publication of this article.

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