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Risk Factors of Symptoms Occurrence in SARS-CoV-2 Infection after Implementing Vaccination Program in Bali

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ABSTRACT

The real-world data demonstrate that COVID-19 vaccines reduce the infection severity, though breakthrough cases still occur with various symptoms. This study assessed the risk factors of symptom occurrence in vaccinated individuals in Bali. This retrospective, case-control study used Pemecutan Kaja Village, North Denpasar's surveillance data, including sex, age, vaccination status, symptom occurrence, and severity. Participants were included if they tested positive for SARS-CoV-2 with a minimum age of 18. There were 592 data on COVID-19 patients; the cases group was symptomatic, and the control group was asymptomatic. From May to September 2021, the vaccination program was implemented in Bali with Sinovac and Astra Zeneca. The risk factor analysis showed that age (OR 2.575, 95% CI 1.376-4.818; p = 0,003) and vaccination status (OR 3.104, 95% CI 2.089-4.611; p = < 0,001) were associated with symptom occurrence in Covid-19. Elderly and unvaccinated subjects have a higher risk of symptom occurrence in SARS-CoV-2 infection. Vaccinations are not fully effective in protecting against infection; however, vaccination can lower the incidence of symptoms and their severity. These findings show the importance of strengthening the vaccination program and adjusting public health interventions to protect vulnerable groups in Bali. Moreover, with these insights, plans and policies can be developed to educate the public regarding the benefit of vaccination in reducing symptoms of infection. A better understanding of the risk factors has implications for prevention and treatment for those with a higher risk of developing severe conditions.

Keywords: Covid-19, Covid-19 vaccines, Symptom occurrence, Risk factors

INTRODUCTION

In January 2020, the World Health Organization (WHO) announced the outbreak of a new coronavirus disease (Covid-19). Due to the ease of transmission, it spread across the globe, posed a significant threat to public health, and became a pandemic. In Indonesia, the government announced the first case of Covid-19 in March 2020 (WHO, 2020a). The development of cases fluctuated; Indonesia has been through 3 peak waves of cases in January, July 2021, and January 2022 with the omicron variant. An extreme upsurge of cases was reported in July 2021, reaching 44.721 new cases and 1.808 deaths daily. Bali is among Indonesia's top 10 provinces with the highest Covid-19 cases. Data per July 31st, 2021, the cumulative cases of COVID-19 reached 76.319 cases and 2.151 deaths as recorded. This phenomenon is due to the high risk of transmission from international and domestic travel from the region (Pemerintah Provinsi Bali, 2021).

Covid-19 has inflicted lameness in all sectors, including public health, economic, industrial, social stability, and tourism (Ophinni et al., 2020). The capacity of health facilities and isolation shelters could not cope with the increasing number of positive cases and facing oxygen shortage (WHO, 2021). One of the strategies that have been implemented is vaccination. Vaccines are considered the most promising approach for curbing the pandemic (Centers for Disease Control and Prevention, 2021a). Some trials and research reported that vaccines effectively prevent infection of Covid-19 (Harder et al., 2021; Lopez Bernal et al., 2021; Olson et al., 2021; Scobie et al., 2021). Infected

patients who were fully vaccinated were less likely to develop a severe illness than unvaccinated patients. Fully vaccinated people were 8 times less likely to be infected and 25 times less likely to be hospitalized and die (Centers for Disease Control and Prevention, 2021b). An effective and safe vaccination program plays a vital role in lowering the range of morbidity and mortality and facilitating psychological and economic recovery (Albalawi et al., 2021; Luxi et al., 2021), especially in Indonesia, which has the highest spike in cases and mortality in Southeast Asia (Ophinni et al., 2020). The risk of SARS-CoV-2 infection in fully vaccinated people cannot be eliminated as long as there is continued community transmission of the virus (Centers for Disease Control and Prevention, 2021b).

Indonesia is a middle-income country where people have varying trust levels of vaccines due to limited information about their effectiveness and safety profile (WHO, 2020b). Many people assume that the vaccine was 100% highly effective and covered up the infection; however, among 1040 fully vaccinated healthcare workers (HCWs), 13 (1,25%) tested positive for COVID-19, with most showing mild flu-like symptoms and some remaining asymptomatic (Cucunawangsih et al., 2021). That research was explicitly designed for health workers who are commonly under 60. A more heterogeneous sample is required to describe the situation in the community, as the incidence and severity of symptoms depend on several factors. SARS-Cov-2 infection is one of the conditions affecting the respiratory tract. Poorer lifestyle habits, including physical inactivity, smoking, and alcohol consumption, elevate the risk of hospitalization with severe symptoms such as pneumonia (Hamer et al., 2020). Studies have shown that individuals over 60 with comorbidities face worse outcomes due to higher angiotensin-converting enzyme (ACE) receptor expression and fewer lung progenitor cells for repair (Bonanad et al., 2020; Luo et al., 2020; Zhang et al., 2021). This study aimed to assess the risk factors of symptom occurrence in COVID-19 after implementing the vaccination program. The present study can describe the natural situation in the community without any restrictions based on age, occupation, lifestyle, or vaccination status. The result of this study might be important for the government to formulate the best approach to implement the strategies to increase vaccination awareness and maintain healthiness.

MATERIALS AND METHODS

Ethics Statement

This retrospective, case-control study used surveillance data from Pemecutan Kaja Village, North Denpasar district, collected by the primary healthcare UPTD Puskesmas II Public health facilities in North Denpasar district. The Indonesian government provides the public with basic healthcare facilities known as *Puskesmas*. Individuals experiencing health issues may seek medical attention at the *Puskesmas*. The patient's medical record data is collected as a record of the patient's treatment history. The government also utilizes the data for health management purposes. Consequently, the collection of patient data is conducted voluntarily. The researcher has obtained permission from the local government to process the medical record data obtained at the health center into research material (certificate from the Government of Denpasar City, National Unity, and Political Agency number B.30.070/517.E/Izin-C/DPMPTSP). Additionally, informed consent is often not required in retrospective studies if the data has been anonymized or taken from public sources (Council for International Organisation of Medical Sciences, 2016).

Sample and Design

We collect data from the medical record in public health facilities from February 22nd to March 31^{st,} 2022. Data, including age, sex, vaccination status, and symptom occurrence from May to September 2021, were extracted, assessed, and cleaned with considerable ethical considerations by the research team. The sample is all data that met the eligibility criteria as follows. Participants were included if they tested positive for SARS-CoV-2 with a minimum age of 18. Vaccination programs for those under 18 years old had just begun when data were collected, so we excluded patients under 18 to avoid bias in this research. Data would be excluded if the information was not complete. Data were considered incomplete if one or more information was missing: age, sex, vaccination status, and symptom category.

The cases group was symptomatic, and the controls were asymptomatic subjects with confirmed SARS-CoV-2 infection. We classified age into two groups: 18-59 years (adult) and ≥ 60 years old (elderly) based on the regulation of the Minister of Health of the Republic of Indonesia No. 25 of 2016.

Vaccination status is divided into vaccinated (partially or fully vaccinated) and not vaccinated. Information about diagnoses and severity of symptoms refers to the provision of the Ministry of Health of Indonesia Hk.01.07/Menkes/4641/2021.

Data Analysis

Univariate analysis was conducted to describe the sex, age, and symptom occurrence. Bivariate analysis using the Chi-Square test was used to assess the differences in the proportion of each parameter (vaccination status, age, and sex) on the symptom occurrence of COVID-19 infection. The Chi-Square test was also used to analyze the effect of vaccination in each subgroup. Quantitative data (age) are grouped into 18-59 years (adult) and ≥ 60 years (elderly). Binary logistic regression is used to simultaneously determine the correlation between the independent variable with a P-value <0.25 and the dependent variable (symptom occurrence of Covid-19). Thus, risk factors that affect the severity of symptoms that occur in COVID-19 patients can be determined. Hosmer and Lemeshow test and AUC calculations were used to assess the accuracy of the equations obtained from the logistic regression results. The calibration of the equation can be considered good if the p-value in the Hosmer and Lameshow test is more than 0.5. Equation discrimination ability was assessed by calculating the area under the curve (AUC). The AUC value is significant if it is greater than 50%, and there is no value of 50% in the AUC confidence interval (Dahlan, 2023). Data was processed using SPSS version 26 with 95% CI.

RESULTS AND DISCUSSION

After the government echoed the call for vaccination, Bali immediately made the priority and carried out the vaccination program. From May to September 2021, Bali had higher proportions of vaccination coverage than other provinces in Indonesia. The program was not running optimally due to several people being unable to receive vaccinations for certain reasons.

Potentially eligible data was taken from surveillance data gathered by UPTD Puskesmas II Denpasar Utara (Public Health Centre in North Denpasar district). Six hundred ninety-seven confirmed COVID-19 patients from Pemecutan Kaja Village, North Denpasar, were recorded between May and September 2021. All data met inclusion and exclusion criteria were analyzed (Figure 1). There was no missing data in this study. Data sources, including sex, age, vaccination status, diagnoses, symptoms occurrence, and severity of symptoms, were available in each medical record.

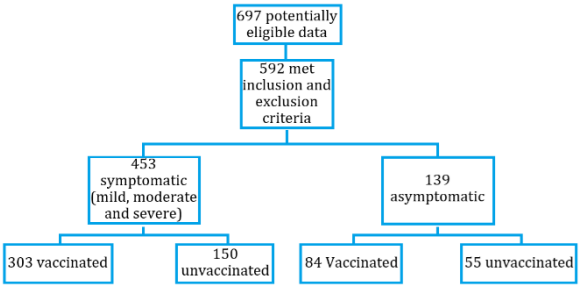

Figure 1. Workflow of sample selection

Sex, Age, and Symptom Occurrence of Sample

The distribution of sex, age, and symptoms occurrence between vaccinated and unvaccinated groups can be described as follows. The patients were predominantly female (52.20%), mostly aged between 18-59 years old (81.93%), and unvaccinated (60.47%). The unvaccinated group remained high due to the eligibility restrictions for vaccine recipients and public concerns about potential side effects post-vaccination of certain vaccines. Data was analyzed by bivariate analysis using Chi-Square with a 95% confidence interval. There were no significant differences between sex in symptom occurrence (p-value = 0.554); however, age (p-value = 0.003) and vaccination status (p-value<0.001) showed significant differences in symptom occurrence.

The unvaccinated group is predominantly female, mostly aged between 18-59 years old. The gender gap phenomenon is due to several limitations, which may explain the high number of unvaccinated females. The possible explanation related to the interaction of vaccines affects conceptions, pregnancy, and breastfeeding. (Toshkov, 2022). This finding is particularly relevant in Bali, where females may face barriers to accessing healthcare for some reasons. Females were more sensitive than males; females reported more adverse reactions to the vaccine.

For this reason, females tend to refuse vaccination (Gebhard et al., 2020). Data from Pfizer vaccines reported that females show more adverse effects (77%) in terms of systemic, dermatologic reactions, and GIT symptoms. Pain at the site injection was the most common adverse reaction (Al-Qazaz et al., 2022). The perception of risk and the possibility of post-vaccination side effects has made people afraid to be vaccinated (Kaplan & Milstein, 2021).

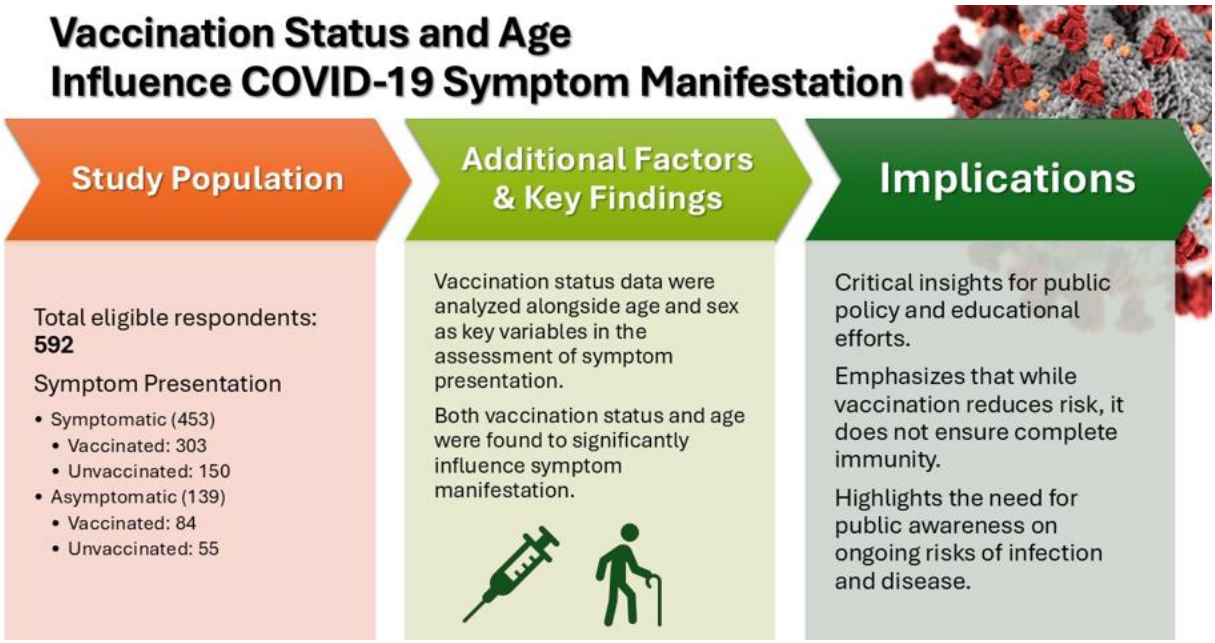

Figure 2. Graphical illustration of the study

Table I. The Correlation between Sex, Age, and Vaccination Status with Symptom Occurrence of Covid-19 Patients

Variable		Asymptomatic		Symptomatic		Σ (total for each variable category)	P-value	OR	CI (95%)	
		n	n / Σ (%)	n	n / Σ (%)				Min	Max
Sex	Male	70	24.7	213	75.3	283	0.554	1.143	0.782	1.672
	Female	69	22.3	240	77.7	309				
						592				
Age	18-59 year	126	26.0	359	74.0	485	**0.003**	2.538	1.373	4.692
	≥ 60 years	13	12.1	94	87.9	107				
						592				
Vaccination status	Vaccinated	84	35.9	150	64.1	234	**<0.001**	3.085	2.084	4.567
	Unvaccinated	55	15.4	303	84.6	358				
						592				

The vaccine's efficacy also plays a vital role in the subject's willingness. The lower efficacy could impact the acceptance and willingness to be vaccinated (Harapan et al., 2020). The willingness to vaccinate increased with age (Dorman et al., 2021), but the exception was for the subjects over 60. The vaccination rates in elderly groups were decreased compared with other groups, in which 56,89% of elderly subjects were reported unvaccinated. Uncontrolled comorbidities are the other reason for the low vaccination rate. Referring to the provision of the Ministry of Health of Indonesia Hk.01.07/Menkes/4641/2021, uncontrolled comorbid conditions were prohibited from being vaccinated. Vaccination in the elderly should be prioritized as geriatric is the leading risk factor for mortality and complications from COVID-19 (Kang & Jung, 2020).

The Correlation of Sex, Age, Vaccination Status with Symptom Occurrence on COVID-19

The effect of each variable on symptom occurrence in COVID-19 patients (Table I) was tested using Chi-Square. 64.1% of vaccinated patients showed a variance of symptoms, dominated by mild symptoms, and the remaining (35.9%) were asymptomatic. All the symptoms were reported less frequent in vaccinated patients.

Table II. The Sub-Group Correlation between Vaccination Status Based on Sex with Symptom Occurrence of Covid-19

Variable		Asymptomatic		Symptomatic		Σ (total for each variable category)	P-value	OR	CI (95%)	
		n	n / Σ (%)	n	n / Σ (%)				Min	Max
Male	Vaccinated	42	34.4	80	65.6	122	**0.002**	2.494	1.435	4.334
	Unvaccinated	28	17.4	133	82.6	161				
Female	Vaccinated	42	37.5	70	62.5	112				
	Unvaccinated	27	13.7	170	86.3	197	**<0.001**	3.778	2.163	6.600
Total						**592**				

Table III. The Sub-Group Correlation between Vaccination Status Based on Age with Symptom Occurrence of Covid-19

Variable		Asymptomatic		Symptomatic		Σ (total for each variable category)	P-value	OR	CI (95%)	
		n	n / Σ (%)	n	n / Σ (%)				Min	Max
≥ 60 years	Vaccinated	42	34.4	80	65.6	122	**0.002**	2.494	1.435	4.334
	Unvaccinated	28	17.4	133	82.6	161				
18-59 year	Vaccinated	42	37.5	70	62.5	112				
	Unvaccinated	27	13.7	170	86.3	197	**<0.001**	3.778	2.163	6.600
Total						**592**				

Table IV. The Risk Factor of symptom occurrence in COVID-19-confirmed patients

Variable	Coefficient	Standard Error	Wald	df	P-Value	OR	CI (95%)	
							Min	Max
Age	0.946	0.320	8.750	1	0.003	2.575	1.376	4.818
Vaccination	1.133	0.202	31.468	1	<0.001	3.104	2.089	4.611
Constanta	0.440	0.143	9.439	1	0.002	1.553		

The vaccinated patient can still get infected after vaccination, which we call post-vaccination infections. Research by Cucunawangsih and colleagues in January 2021 stated that the healthcare workers who had received two doses of Sinovac vaccines remained at risk of acquiring infection, especially in Indonesia, where the number of cases was still fluctuating in that period (Cucunawangsih et al., 2021). However, the likelihood of severity is less in vaccinated patients (Antonelli et al., 2022). Vaccines induce the humoral immune response, which confers against SARS-CoV-2 infection and antibody response to prevent the physical deterioration of patients (Dong et al., 2020). Two doses of vaccines give protection and reduce the risk of infection. Patients had received two doses of vaccines have a lower possibility and risk of COVID-19 hospitalization (Gomes et al., 2021). The research result suggests that the vaccinated subject's risk of symptom occurrence was reduced.

Both males and females showed the same symptom occurrence level in this research. They had the same susceptibility to symptom occurrence, but males were more prone to severe conditions (Jin et al., 2020). A study from Zhongnan Hospital in Wuhan showed that males were one of the risk factors for prolonged symptoms of COVID-19 (Mo et al., 2020). The male has a higher fatality rate due to the incidences of cardiopulmonary disease in terms of smoking habits (Chen et al., 2020). Smoker undergoes impoverished immunity, which may contribute to the risk of severe symptoms of COVID-19 (Rahman & Sathi, 2021).

Symptoms of COVID-19 were more prevalent in the elderly than in another group. 87,9% of patients over 60 reported having symptoms of COVID-19 between mild to severe; this number is higher than younger adult patients. Aging has been significantly associated with worse outcomes, as comorbidities often increase. Elderly patients are more vulnerable to infection due to impairment of the function of innate immune cells. This phenomenon increases the likelihood of a dysregulated immune response that leads to cytokines being released, resulting in a cytokine storm. The high level of cytokines indicates a poor prognosis for COVID-19 (Kang & Jung, 2020). A

study on older adults in Wuhan reported that the elderly had elevated levels of blood IL-6, high sensitivity cardiac troponin I, lactate dehydrogenase, and lymphopenia, which exhibited more severe symptoms than younger adults (Zhou et al., 2020).

In this research, we are subgrouping the sex and age based on vaccination status to analyze the possibility of each variable affecting the symptom occurrence (Table II and Table III). The odds of Vaccinated females being asymptomatic in COVID-19 infection is 3.778 times higher than that of unvaccinated females. In addition, the odds of vaccinated males being asymptomatic for COVID-19 infection is 2.494 times higher than unvaccinated males. Vaccinated females exhibit a lower percentage of symptoms than vaccinated males. Once vaccinated, females will have a higher antibody response to the virus and a greater humoral and cell-mediated immune response to the virus. They will develop a higher antibody response than males (Gebhard et al., 2020). The infection occurs when the SARS-CoV-2 virus enters the body and attaches and binds with the ACE2 receptor. Some research reported that the expression of ACE2 was frequently higher in males due to the ability of testosterone to maintain ACE2 levels. Meanwhile, estrogen reduces ACE2 expression. The phenomenon aligns with case fatality in males than females (Jin et al., 2020; Kopel et al., 2020). Both vaccinated males and females showed a lower number of symptoms than unvaccinated.

Elderly subjects are more likely to show several symptoms than adults (Table III). However, once vaccinated, it would give protection and reduce the severity and hospital admission (Ranzani et al., 2021). The immune system plays a vital role in responding to SARS-CoV-2 infection, but its effectiveness declines with age. Aging is associated with immunosenescence, characterized by a gradual deterioration of both innate and adaptive immune responses (Barbé-Tuana et al., 2020). It reduces the ability of the body to respond quickly to new infections, including SARS-CoV-2. This phenomenon occurs, resulting in a higher risk of severe illness and mortality among the elderly. These factors contribute to prolonged infection duration, increased viral replication, and a greater likelihood of complications. The weak immune responses in older individuals may also delay viral clearance and increase the risk of severe outcomes, including respiratory distress and hospitalization. However, COVID-19 vaccines have been shown to mitigate these risks by stimulating a protective immune response in older adults. Although vaccine-induced immunity in the elderly may not be as strong as in younger populations, it significantly reduces symptom severity, prevents progression to severe illness, and lowers the need for hospital admission. Therefore, ensuring high vaccination coverage among the elderly is crucial to mitigating the effects of immunosenescence and protecting this vulnerable population from unfavorable outcomes (Hu et al., 2023).

Risk Factors of Symptom Occurrence on COVID-19 Patients

In the risk factor analysis (Table IV), age and vaccination status were significantly associated with symptom occurrence of Covid-19. The equations model to predict the occurrence of symptoms obtained from the results of the logistic regression test are as follows:

Y (occurrence of symptoms) = 0.440 + 0.946 (age) + 1.133 (vaccination status)

The Hosmer and Lameshow test showed a p-value of 0.812. The P-value of the Hosmer and Lameshow test is more than 0.05, so it can be stated that the equation has a good calibration. The AUC value of the resulting equation was 66.4% (95% CI: 61.4-71.5). Therefore, the AUC of the resulting equation is statistically significant. The equation has a discrimination capability.

Vaccination is essential in preventing the infection and severity of the symptoms. Patients who received two doses of vaccines were less likely to report symptoms less severe than those unvaccinated (Kuodi et al., 2022; Meggiolaro et al., 2022). The tendency of severe outcomes was significantly related to age. Older adults have a higher risk of hospitalizations at least five times than patients aged less than 45 years (Wingert et al., 2021). The elderly have impaired memory T cells and efficient B cells, implying a decrease in vaccine effectiveness (Perrotta et al., 2020). The elderly usually have chronic illnesses, and when they get infected, they are more susceptible to symptoms than adults (Guo et al., 2020).

Being vaccinated does not guarantee immunity from COVID-19 infection. However, vaccination helps to reduce the symptom occurrence, and the risk of hospitalization compared to unvaccinated individuals. Some previous studies revealed that vaccinated

individuals are still susceptible to infection; this study highlights the risk factors among vulnerable groups that may lead to developing symptoms. These findings might also have implications for preparing strategies for protecting the frail and elderly populations to prevent unfavorable outcomes.

Strengths and Limitations of Study

The study has several limitations. We could not include several conditions that might affect the symptom occurrence (comorbidities, BMI), details of the vaccination status (fully or partially vaccinated), and the variance of vaccine received on each subject. Furthermore, using voluntary sampling may lead to underreporting, resulting in a sample that does not accurately reflect the population. Apart from limitations, our study also has strengths. Data was taken at the beginning of the pandemic. This study uses case-control methods, which are compatible with new cases like COVID-19 and allow for assessment of the risk factor of the outcome. The sample may represent the infection status of a particular region, and we used a total population sample with COVID-19 infections from May to September 2021. So, the data can show the natural conditions that occurred at that time.

CONCLUSION

Vaccination status and age are significant risk factors in predicting symptomatic Covid-19 infections. Vaccinated subjects are less likely to undergo symptoms than unvaccinated. Moreover, the elderly are more likely to develop symptomatic Covid-19 infection. Although gender did not significantly affect the occurrence of symptoms of COVID-19 infection, vaccinated women showed better protection than vaccinated men. Vaccinations were not 100% effective in protecting people from infection, but vaccination programs conducted in Bali can reduce the incidence of symptom occurrence and its severity. These findings can provide insights for public policy and educate the community on the impact of vaccines in reducing symptoms and mortality. It is conceivable that the government may hypothesize that the vaccine administration may elicit disparate effects in specific demographic groups. The study's findings may inform stakeholders in developing strategies to enhance patient health literacy by elucidating the potential risk factors influencing the program's efficacy across diverse groups.

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CONFLICT OF INTEREST

The authors have no conflict of interest associated with the material presented in this paper.

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