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Stress Influence on the Adverse Events Emergence after Coronavirus Disease (COVID-19) Vaccination

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Abstract: An individual's response to a threatening alteration is called stress, whereas a stressor is defined as a personal reaction to an external event. Since the COVID-19 disease pandemic was first announced, vaccination has become one of the government's controls and prevention measures to overcome the pandemic. Prolonged stress can lead to the inefficacy of the vaccine, thus promoting more immediate and transient vaccine adverse events. This study aimed to seek the relationship between stress and adverse event incidence after COVID-19 vaccination. The cross-sectional study was conducted on 244 respondents (18 – 40 years old) in Depok City, Indonesia. Stress levels were assessed by the Perceived Stress Scale, while Side Effects of COVID-19 vaccination and Opinion Survey were collected immediately after the vaccination. The data were analyzed using the Chi-Square test regarding stress on the adverse events after COVID-19 vaccination with a significance level of $p < 0.05$, p-value = 0.000. The relationship between sex and age with the incidence of the adverse event after COVID-19 vaccination obtained p-values of 0.951 and 0.490, respectively. This study showed that the incidence of the adverse event after COVID-19 vaccination was statistically related to stress but not sex and age.

Keywords: stress level; COVID-19 vaccine; side effects.

1. Introduction

Since 2020, the world has struggled to overcome a viral respiratory disease, called coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2. The world started focusing on Hubei province in the People's Republic of China in October 2019, as this was the first encounter, even though later, scientists found coronavirus in several wastewater samples in Spain in March 2019 [1]. Control efforts to sluggish the transmission of COVID-19 disease and reduce soundness impacts have been carried out by various countries in the world, including Indonesia [2], by implementing social distancing, partial and or complete lockdowns, school or work activities were done from home, closing places of business, and the urge to wear masks in public places [3].

Forms of COVID-19 that spread rapidly have emerged over the last two years. An increase in the incidence of COVID-19 has been reported as soon as the re-opening of community and economic activities, and other new variants are likely to emerge in the future [4]. Therefore, there is an urgency for long-range prevention efforts, and vaccination is one of

the effective and efficient means to protect the public from the effects of SARS-CoV-2 [5,6]. In January 2021, Indonesia began implementing the COVID-19 vaccination program, and almost all developed vaccine types, such as inactivated whole virus, protein subunit, or viral vector, are used nowadays [7,8]. The vaccine's efficacy sometimes is lower than expected, as it may depend on the person who accepts the vaccine [9,10].

As the pandemic was declared by WHO in March 2020, this disease has already spread through more than 200 countries, thus causing confusion and stress to the population worldwide. Stress is the body's reaction to tension or stressors often set off while encountering new, unforeseen, or compromising circumstances [11]. Stressors can incorporate mental, social, and psychological factors that may extensively impact the immune response to the vaccine [12]. Psychological factors yield a counteracting agent reaction toward immunizations, especially in younger people [10,13]. There is proof that as well as lessening the viability of immunizations, stress can set off extra brief and transitory secondary effects, including fatigue and a terrible attitude [9,14]. One study from the University of Ohio revealed that when an individual is more worried and restless about getting a COVID-19 inoculation, it might take more time for antibodies to create, and incidental effects might happen after immunization [10,15].

Regarding the limited data about the effect of stress on adverse events after COVID-19 vaccination, we aim to carry out this research on adult people confirming the occurrence of adverse events after vaccination as the recipients went through the process of vaccination under stress.

2. Materials and Methods

2.1. Study population and ethics.

The research was conducted for 3 months, from August until November 2021. As many as 244 persons, 85 men and 158 women aged 18–40 years old, and have received two doses of the COVID-19 vaccine from four villages in Limo sub-district, Depok city, Indonesia, were recruited as respondents. This study received ethical approval from the Trisakti University Medical Research Ethics Commission (protocol code 56/KER-FK/IX/2021).

2.2. Methods.

The stress level was assessed using questionnaires according to Hary & Pricianee [7], including the perceived stress scale. Meanwhile, the events subsequent to getting a COVID-19 vaccination were assessed Side Effects and Opinions Following COVID-19 Vaccination.

2.3. Statistical analysis.

The data were statistically analyzed using the Chi-square test to see whether there is a relationship between stress and adverse events after COVID-19 vaccination. Statistical analysis was performed using SPSS 25.0 for Windows software with a 95% confidence level ($a = 0.05$). Results were considered statistically significant at $p < 0.05$.

3. Results and Discussion

As of 2nd February 2022, more than 4.3 million people in Indonesia have been diagnosed with coronavirus 2019 (COVID-19), and over144,000 of them passed away [16]. A

powerful and effective vaccine to save many lives consistently is one method to overcome this pandemic [17]. Accepting vaccines in the community is an important component of achieving high vaccination coverage [18]. Table 1 shows that women and the middle-aged population are more likely to comply with the government's regulation in receiving a full vaccination package.

It has been known widely that sex differences stand as one factor that may affect the immune response [19], in addition to natural elements and psychosocial factors [20]. We found no significant relationship between sex and the incidence of adverse events after COVID-19 vaccination (p = 0.951). The Centers for Disease Control and Prevention (CDC) reports that most responses to COVID-19 immunization are not serious, and over 79% of those happen in females [21].

Table 1. Characteristic of Respondents.

Variables	SE positive (%)		SE negative (%)		Total	p-Value
Sex					N (%)	
- **Male**	31	35,23	57	64,77	88 (36,07)	0,951[a]
- **Female**	54	36,1	102	65,38	156 (63,93)	
Age						
- **18- 39**	27	28,12	69	71,87	96 (39,34)	
- **40-59**	65	45,77	77	54,22	142 (58,20)	0,490*
- **>60**	5	83,33	1	16,67	6 (2,46)	
Stress Level						
- **Low**	40	58,82	28	41,18	68 (27,87)	
- **Moderate**	48	27,91	124	72,09	172 (70,49)	0,000*
- **Severe**	1	25,0	3	75,0	4 (1,64)	

[a] *Chi-Square test*, p < 0,05

[*] *Mann-Whitney test*, p < 0,05

Vaccination is a way to activate the body's immune system by introducing a weakened pathogen or a part of the pathogen to the human's body, but sometimes there would be side effects following vaccination. This situation happens when the inflammatory response is exceeding than expected. Various studies showed that women generally have stronger and healthier immune systems, which leads to higher antibody production, making women more susceptible to the side effects of the COVID-19 vaccine than men [20,21]. A study by Gee et al. [22] analyzed the safety data of more than 13 million doses of the first COVID-19 vaccine administered in the United States of America (USA) alone. This study concluded that side effects appeared more in women than men, even though the vaccine was given to only 61 women. Ilardi et al. [23] concluded in a research report that COVID-19 infection risk factors also comprised sex and age.

Age is one important factor determining vaccine response, as age triggers immune response modification. This study's findings showed no statistically significant relationship (p = 0.490) between age and adverse events. Unfavorable occasions that happen after COVID-19 immunization at all ages are generally similar, and there is no distinction in either onset or severity. We also found a smaller portion of the respondents aged > 60 who experienced adverse events after the COVID-19 vaccination compared to younger adults. Beatty *et al*. also reported the same results, as adverse events were more common in younger respondents [24].

Another significant characteristic of the maturing immune system is a low-level pro-inflammatory cytokine, as can be seen in older people, contributing to the vulnerability of infection. This phenomenon also leads to a lack of response to vaccination [21,25]. Younger adults generally have a more robust immune system, resulting in a firmer immune response to vaccines and a higher-up of adverse events. In contrast, one study concluded that the frequency of adverse events was the same across the age groups, but the tendency increased along with

age [18]. Another preceding study further stated that there was no relation between age and the incidence of adverse events after COVID-19 vaccination [26].

Albeit the security and viability of several COVID-19 immunizations have been validated, the people in the community have many considerations regarding the adverse effects. Those concerns greatly impacted public readiness to have vaccines, thus lowering vaccination coverage [27,28].

Even though stress is a normal defense mechanism in humans, excessive stress could harm physical health by inhibiting the human immune response [29]. Psychological stress or anxiety interfacing with COVID-19 immunization needs to be lowered for self-confidence boosting and forbearance of vaccination [30,31]. Some studies showed that stress is one of the variables that can repress the immune reaction in vaccination, thus simultaneously triggering side effects following COVID-19 vaccination from mild to moderate levels [10,15]. One foregoing study stated that stress is related to the beginning of adverse effects after the COVID-19 vaccination [26], as another study revealed that the adverse effects might be varied from lower efficacy to nocebo effect [32] due to disruption and unbalanced binding of hormones and receptors, which leads to glucocorticoid receptor resistance, and at the end which will affect the body's immune system. The nocebo impact is a negative response characterized by hostile side effects and mostly triggered by a negative mindset that an undesirable event will occur following vaccine management or other clinical intervention. Nocebo effect could be systemic or just local symptoms, including local pain at the injection site, fatigue, and headache [32,33].

Similar to the past report, the respondents' anxiety in this examination showed a huge relationship with the occurrence of unfriendly occasions after COVID-19 immunization. Stress and negative contemplations can influence the immunization reaction, particularly the lower neutralizer reaction after inoculation, which can fortify and stretch out the intense provocative response to the antibody, thus invigorating the beginning of unfavorable occasions after COVID-19 inoculation [11,34,35].

4. Conclusions

This research reaffirms that stress is related to the frequency of adverse events following COVID-19 vaccination. Sex and age are believed to have a role in influencing the immune system response; however, in this research, there was no significant relationship between sex and age with the incidence of adverse events after COVID-19 vaccination. A better understanding of other psychological factors is needed to adjust the vaccination implementation strategy to get high coverage of any vaccination.

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Conflicts of Interest

The authors declare no conflict of interest.

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