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Sinovac Adverse Event Following Immunization (AEFI): Correlation to Gender and History Aefi in Students

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Abstract

As one of the nations impacted by the COVID-19 pandemic, Indonesia adopting a vaccination policy for its population. After vaccination, there will be a chance to have an AEFI that influenced by gender and the history of AEFI from the previous vaccination. This research designed using a cross-sectional approach. Sample is taken from 365 students of Tadulako University. The questionnaire was developed using information based on Indonesia Ministry of Health and the World Health Organization. All data collected was analyzed using the Contingency Coefficient test. There was a significant relationship between gender and pain (p = 0.004, r = 0.148), redness (p = 0.041, r = 0.107), swelling at the injection site (p = 0.037, r = 0.109), cellulitis (p = 0.037, r = 0.109), and headache (p = 0.006, r = 0.143). There was a significant relationship between history of AEFI and pain (p = 0.000, r = 0.182), redness (p = 0.000, r = 0.274), swelling at the injection site (p = 0.001, r = 0.178), cellulitis (p = 0.000, r = 0.249), fever (p = 0.000, r = 0.382), myalgia (p = 0.000, r = 0.239), arthralgia (p = 0.000, r = 0.268), asthenia (p = 0.000, r = 0.254), and headache (p = 0.000, r = 0.218). More students did not get AEFI than did. AEFI was more common experienced by females and students who had no previous history of AEFI. Most of all AEFI will improve in less than a day.

Keywords: Adverse Event Following Immunization (AEFI), COVID-19 Vaccine, Gender, SinoVac

1. Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by a corona virus that was found in 2019. Most patients infected with the COVID-19 virus will develop mild to moderate respiratory illness and will recover without the need for specific treatment. People over the age of 65, as well as those suffering from medical conditions such as cardiovascular disease, diabetes, chronic respiratory illness, and cancer, are more prone to encounter severe symptoms.[1]

Patients who tested positive for COVID-19 on December 31, 2020 increased by 8.074 cases. The total number of positive confirmed patients registered since the first case until December 31, 2020 was 743.198. As long as there is no definite cure for COVID-19, the COVID-19 vaccine is one of the safest and most efficient approaches to avoid this condition.[2]

The implementation of the COVID-19 vaccination in Indonesia has been carried out since January 2021, divided into 4 stages, and is expected to be completed in March 2022. The number of confirmed COVID-19 cases per day peaked at 14.518 cases per day during the start of the COVID-19 vaccination program. The number of confirmed COVID-19 cases is slowly reducing as the COVID-19 vaccination program continues. On April 6, 2021, the number of COVID-19 instances per day decreased to 4.549.[3]

The COVID-19 vaccine, like other vaccines, protects the body from COVID-19 infection by creating or boosting particular immunity in the body. Sinovac is a COVID-19 vaccine that is used in Indonesia. Sinovac is manufactured with aluminum hydroxide as an adjuvant and is made from inactivated SARS CoV-2 virus. Most of the adverse events following immunization (AEFI) caused by

these vaccines are mild. When compared to other COVID-19 vaccine candidates, such as viral vector vaccines or DNA or RNA vaccines, Sinovac has a lower incidence of fever after vaccination.[4]

Zhang et al.[4] found that two doses of Sinovac at varied dosages and dosing schedules were well tolerated and highly immunogenic in healthy adults aged 18–59 years. The incidence of adverse events following immunization (AEFI) in the Sinovac group was similar at 3 μg and 6 μg dosages, and no dose-related safety issues were identified.

Gender differences can have an impact on immunological response and adverse events following immunization (AEFI). Male and female immune responses differ, according to clinical data on a variety of vaccines. Although females have a greater immune response than males, AEFI is more common and severe in females than in males. In addition to gender, the AEFI in people receiving the COVID-19 vaccine is influenced by previous AEFI history[5]. As a result, the purpose of this study is to examine the association between history of AEFI vaccination and gender with AEFI in the COVID-19 vaccine in students of Tadulako University.

2. Material and Methods

This is a quantitative study with an observational analytical research design. Using a cross-sectional approach, the study design is carried out once in a while with measurements or observations carried out. This study was carried out at Tadulako University during July-August of 2021. The research sample consists of students at Tadulako University. The determination of the minimum number of samples used the Slovin formula and obtained a minimum sample of 363 students. The sampling technique used was purposive sampling. This study used a questionnaire as an instrument to collect data. The questionnaire was distributed and filled out by students using a Google form. The inclusion criteria for this study were students of Tadulako University who were vaccinated using the SinoVac/CoronaVac/BioPharm vaccine and students who had completed vaccination up to stage 2. The exclusion criteria for this study were students of Tadulako University who answered "don't know" to questions about the history of AEFI in previous vaccinations. The questionnaire was developed by researchers with reference to the adverse event following immunization (AEFI) COVID-19 vaccine based on Indonesian ministry of health and the World Health Organization.[6,7] After all the data is collected and coded, the researcher will enter the data into a statistical application, namely SPSS. Bivariate analysis to determine the relationship between gender and adverse events following immunization (AEFI) COVID-19 vaccine in students of Tadulako University used a non-parametric statistical test, namely the Contingency Coefficient.

3. Results

This study has a sample of 365 students. The male sample there are 87 students, while the female sample there are 278 students (Figure 1). A total of 146 students (40%) from the total sample experienced adverse events following immunization (AEFI) and the remaining 219 students (60%) from the total sample did not experience adverse events following immunization (AEFI) (Figure 2).

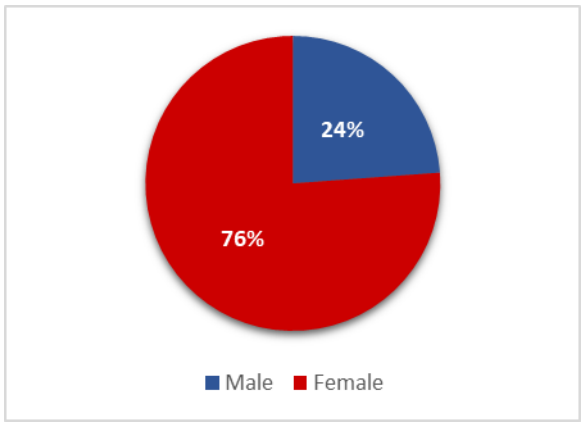


Figure 1. Gender Distribution

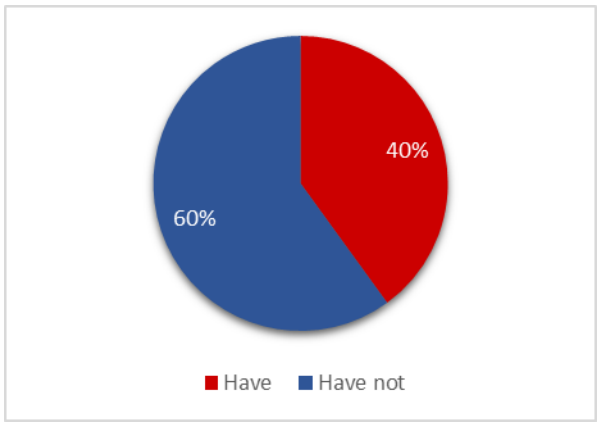
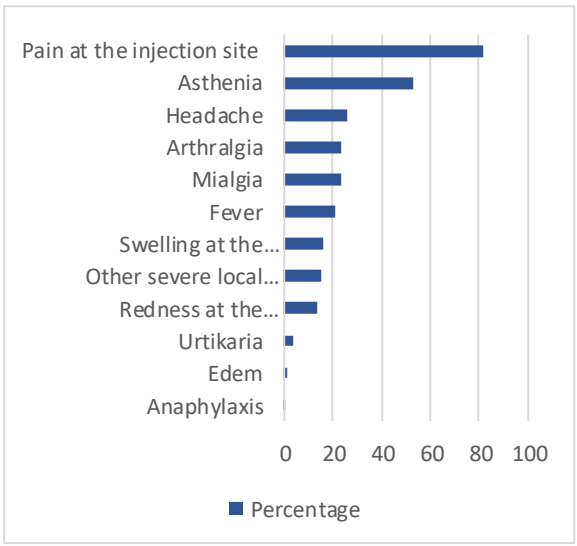
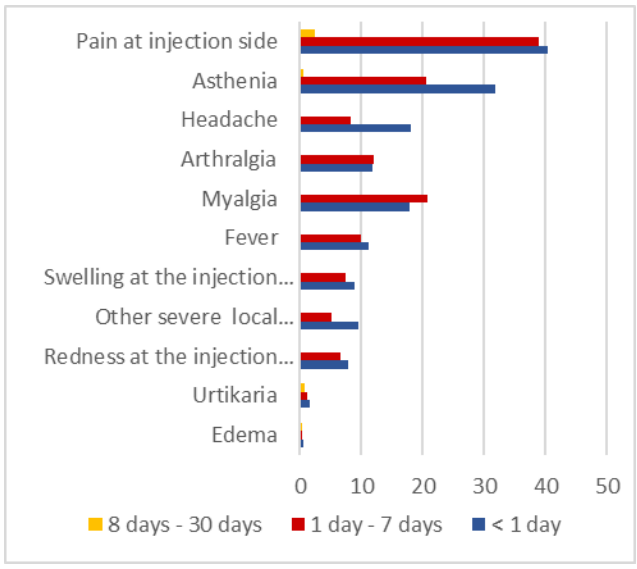


Figure 2. History of AEFI Distribution

In this study, the most common AEFI that students experienced were pain at the injection site (81.6%) and asthenia (53.2%). More students experienced several AEFI of the SinoVac vaccine for less than a day. Neverthless, in this study there was also an anaphylactic reaction, but only experienced by 1 out of 365 students (0.5%) (Figure 3a and 3b). Some students mentioned experiencing other symptoms, such as increased appetite and sleepiness.



(a)



(b)

Figure 3. (a) AEFI of SinoVac Vaccine Distrribution; (b) Duration of SinoVac AEFI Distribution (Percentage)

In this study, there was a significant relationship between gender and pain at the injection site (p = 0.004), redness at the injection site (p = 0.041), swelling at the injection site (p = 0.037), other severe local reactions, such as cellulitis (p = 0.030), and headaches (p = 0.006). Adverse events following immunization (AEFI) were more common in female than male students and all of the reactions had a very weak correlation with gender (Table 1). There was also a significant relationship between the history of AEFI and pain at the injection site (p = 0.000), redness at the injection site (p = 0.000), swelling at the injection site (p = 0.001), and other severe local reactions such as cellulitis (p = 0.000), fever (p = 0.000), myalgia (p = 0.000), arthralgia (p = 0.000), asthenia (p = 0.000), and headaches (p = 0.000). Pain and swelling at the injection site had a very weak correlation with the history of AEFI. Meanwhile, redness at the injection site and other severe local reactions such as cellulitis, fever, myalgia, arthralgia, asthenia, and headache had a weak correlation with the history of AEFI (Table 2).

Table 1. Correlation Between Gender and SinoVac AEFI

		Gender		P-value	r
		Male	Female		
Pain at the injection site	Yes	62	236	0,004	0,148
	No	25	42		
Redness at the injection site	Yes	6	43	0,041	0,107
	No	81	235		
Swelling at the injection site	Yes	8	52	0,037	0,109
	No	79	226		
Other severe local reaction such as cellulitis	Yes	7	49	0,030	0,113
	No	80	229		
Fever	Yes	15	62	0,313	0,053
	No	62	216		
Myalgia	Yes	29	110	0,296	0,055
	No	58	168		
Arthralgia	Yes	18	69	0,430	0,041
	No	69	209		
Asthenia	Yes	45	149	0,760	0,016
	No	42	129		
Headache	Yes	13	83	0,006	0,143
	No	74	195		
Urticaria	Yes	5	8	0,208	0,066
	No	82	270		
Edema	Yes	1	3	0,956	0,003
	No	86	275		

Table 2. Correlation Between History of AEFI and SinoVac AEFI

		History of AEFI		P-value	r
		Yes	No		
Pain at the injection site	Yes	132	166	0,000	0,182
	No	14	53		
Redness at the injection site	Yes	37	12	0,000	0,274
	No	109	207		
Swelling at the injection site	Yes	36	24	0,001	0,178
	No	110	195		
Other severe local reaction such as cellulitis	Yes	39	17	0,000	0,249
	No	107	202		
Fever	Yes	61	16	0,000	0,382
	No	85	203		
Myalgia	Yes	77	62	0,000	0,239
	No	69	157		
Arthralgia	Yes	56	31	0,000	0,268
	No	90	188		
Asthenia	Yes	101	93	0,000	0,254
	No	45	126		
Headache	Yes	56	40	0,000	0,218
	No	90	179		
Urtikaria	Yes	8	5	0,106	0,084
	No	138	214		
Edema	Yes	3	1	0,151	0,075
	No	143	218		

4. Discussion

The purpose of this study is to determine the effect of gender and AEFI history on the number of AEFI events after the Covid-19 vaccination. This study included a group of students aged 17 to 25 who had been vaccinated with Sinovac/Corona Vac/Biopharm vaccine. Gender differences in relation to current AEFIs have a significant correlation with some local and systemic AEFI reactions, as well as previous history of AEFIs in relation to current AEFIs. The correlation strength between gender differences and the current AEFI is very weak, while the correlation strength between the previous history of AEFI and the current AEFI is weak and very weak.

Vaccination is one solution that is considered capable of overcoming the COVID-19 pandemic. Various institutions in all countries are trying to create vaccine variants with their respective characteristics and efficacy. As one of the countries affected by the COVID-19 pandemic, Indonesia responded to the dynamics of this pandemic by issuing a vaccination policy for all its citizens. After vaccination, we can also get medical events which are commonly called adverse events following immunization (AEFI). AEFIs can be in the form of vaccine effects or side effects, toxicity, sensitivity reactions, pharmacological effects or coincidental program errors, injection reactions or causal relationships cannot be determined. AEFI can occur within 1 month after vaccination.[3]

Adverse events following immunization (AEFI) that may occur after COVID-19 vaccination are almost the same as with other vaccines. The AEFI reaction is divided

into 3, namely: local reactions, systemic reactions, and other reactions. Local reactions consist of pain, redness, and swelling at the injection site, or other severe local reaction, such as cellulitis. Systemic reactions consist of fever, myalgia, arthralgia, asthenia, and headache. Other reactions consist of urticaria, edema, anaphylactic reactions, and syncope.[3]

All vaccinations have the ability to activate pattern-recognition receptors (PRRs), which lead to the synthesis of various mediators. Immune cells such as monocytes, macrophages, mast cells, and dendritic cells, as well as resident stromal cells including keratinocytes and skeletal muscle cells, all express PRRs. Resident cells, particularly macrophages and mast cells, are critical target cells that start the immune response within minutes after vaccination by producing proinflammatory cytokines, chemokines, complement cascade effectors (C3a and C5a), and vasodilators such as vasoactive amines and bradykinin. Vasodilators and the chemokine gradient increase blood cell recruitment, but they also cause redness and edema. Extravasation allows blood-borne neutrophils, monocytes, and lymphocytes to attach to artery walls and aggregate at the site of damage. These immune cells may contribute to peripheral nociceptive sensitisation by secreting soluble substances like cytokines, prostaglandins, or ATP and interacting directly with nociceptors (sensory neurons that respond to potentially harmful stimuli) to induce pain if the pain threshold is reached. Fast-conducting myelinated neurons transmit pain sensations (the fast neural pathway).[8]

The mediators and products of inflammation at a specific place in the body may enter the circulation and impact other body systems, resulting in systemic adverse events. These systemic pyrogenic substances, together with pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and adherent monocytes, cause cross-talk between the immune response and the central nervous system via receptors on the vagus nerve, at the blood-brain barrier and perhaps inside circumventricular organs. The induction of the inducible enzymes cyclooxygenase-2 and microsomal prostaglandin E synthase-1 by these signal molecules results in elevated intracerebral levels of prostaglandin E2, the critical terminal mediator of raised body temperature and other systemic symptoms like headache, myalgia, and chills (or "sickness syndrome") within the brain. Finally, intracerebral prostaglandin E2 stimulates neural circuits that regulate autonomic and behavioral responses, including peripheral vasoconstriction, metabolic heat behaviour, shivering (‘chills'), warmth-seeking behaviour, and results in an increase in body temperature.[8]

Adverse events following immunization (AEFI) can be affected by gender differences. Clinical research that has been done on many vaccines shows that there are differences in the immune responses between males and females.[5] Xiong et al. [9] mentioned that allergic reactions and injection site reactions have been reported to be female-predominant and are thought to be related to higher immune/inflammatory responses in females.[10] According to the previous studies by Harris et al.[10], Hervé et al.[8], and Marques et al.[11], it is mentioned females made up the majority of AEFI reports. But in the yellow fever vaccine (YFV), there was no difference in AEFI reporting between males and females when comparing the most frequently reported systemic and local AEFI.[12]

Higher immune/inflammatory responses may be modulated by sex hormones, like androgens and high dosages of oestrogen. It has been demonstrated to inhibit immunological responses, cytokine levels,

and cause immunosuppressive.[8] Sex steroids have such a strong influence on the immune system, hormonal changes during the female menstrual cycle influence cyclical changes in immune function with pronounced fluctuations in immune cell numbers. These changes can increase the numbers of Treg cells and prostaglandin E2. Treg cells have a role in regulating or suppressing other cells in the immune system. Meanwhile, prostaglandin E2 is a potent inflammatory mediator that is generated by cyclooxygenase 2 (COX2).[13]

The differences in skin thickness, blood flow, and nervous system anatomy between males and females may also have caused the development of injection-site inflammation in females.[8] As well as variations in body mass and muscle/subcutaneous fat distribution, the latter in relation to injection site reactions specifically.[10]

To reduce the risk of adverse events following immunization (AEFI), we have to pay attention to whether the recipient is included in the risk group. One of those included in the risk group is a child who has had an adverse reaction to the previous vaccination.[12]

According to a previous study by Zafack et al.[14], after reimmunization of individuals who had AEFI, the probability of significant AEFI (anaphylaxis, seizures, or apnea in term babies) recurring was minimal (<1%). The recurrences were typically less severe or comparable to the initial episode. AEFI or side effects might manifest as unwanted signs, abnormal laboratory findings, symptoms, or illness.

These are several categories of AEFI: vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, immunization anxiety-related reaction, and coincidental events. Vaccine product-related reactions can cause adverse events following immunization (AEFI) triggered by the vaccine itself, due to one or more of the intrinsic characteristics of the vaccine product. A vaccine quality defect-related reaction can cause adverse events following immunization (AEFI) triggered by one or more quality defects in the vaccine product, including the delivery kit provided by the manufacturer. Immunization error-related reactions can cause adverse events following immunization (AEFI) triggered by improper handling, prescribing or administration of vaccines. Immunization anxiety-related reactions can cause adverse events following immunization (AEFI) arising from anxiety about vaccination. For example, an adolescent syncope due to fear, pain, phobia, heat, and hyperventilation after getting vaccinated. Coincidental events can cause adverse events following immunization (AEFI) due to other factors than the vaccine product, immunization errors or anxiety about immunization.[6]

Previous study by Joshi et al.[15] has shown that there are differences in AEFI with age, so it is possible that the results of this study will be influenced by the age range as well. Because older people have lower levels of CRP, IL-10, and IL-6 after vaccination, their AEFI is also lesser response than younger people. However, because we did not compare AEFI across ages in this study, it is difficult to determine the effect of age on AEFI.

This study has some limitations. First, we have only one group age, which starts at 17 years old and goes up to 25 years old. Due to this age range, it is difficult for us to determine AEFI in other age ranges. Second, we only use one population, students at Tadulako University, which means we cannot explain the AEFI in terms of the larger population. Third, we use cross sectional approach as our method in this research. Cross-sectional approach have lower

accuracy when compared to cohort approach.

5. Conclusions

After the COVID-19 vaccination, more students did not get AEFI than did. The most common AEFI experienced by students who have received COVID-19 vaccine were pain at the injection site and asthenia. Anaphylactic reaction was the least AEFI that experienced by students who have received COVID-19 vaccine, that is only happen in 1 out of 365 students. Most of all AEFI will get better in less than a day. AEFI more experienced by female students and students who did not have a history of AEFI in previous vaccinations. In view of these findings, we recommend that further studies should deeply discuss about different ages and other intrinsic factors, other than gender, such as ethnicity, body mass index, circadian cycle, and psychological stress.

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