Original Article

# Adverse Events Following Immunization of mRNA and Inactivated Vaccines Against COVID-19 at Universitas Indonesia Hospital: A Cross-Sectional Study

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## Abstract

**Background:** The coronavirus that causes severe acute respiratory syndrome (COVID-19) is coronavirus 2 (SARS-CoV- 2). This virus has caused a global pandemic. The adverse impact of this virus in the past two years has resulted in efforts to build herd immunity through vaccination. This study aimed to identify the side effects after getting the *Pfizer* and *Sinovac* vaccines at the Universitas Indonesia Hospital and the risk factors for Adverse Events Following Immunization (AEFI).

**Methods:** This observational study used a descriptive, non-experimental method with a cross-sectional design. Google Forms was used to collect data.

**Results:** The onset of AEFI symptoms ranged from 15 minutes to 24 hours. The common AEFI symptoms were pain at the injection site, fatigue, muscle aches, and joint pain. The AEFI severity was mostly at the mild level, and only a few participants took medication. Female participants, participants with comorbidities and allergies, previous medication histories within the last 6 months, and those with experience of COVID-19 had a higher risk for AEFI with a statistically significant effect ($P$ <0.005).

**Conclusion:** This study revealed that *Pfizer* and *Sinovac* COVID-19 vaccines were safe to administer as the AEFIs were mostly mild and automatically disappeared and decreased after 1 to 3 days.

**Keywords:** AEFI, COVID-19, Pfizer, Sinovac, vaccine

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## INTRODUCTION

The coronavirus that causes severe acute respiratory syndrome (COVID-19) is coronavirus 2 (SARS-CoV-2). Global pandemic brought on by this virus. There were 27 people with pneumonia in Wuhan, Hubei Province, China, in late 2019. The virus spread quickly across the globe.[1] Indonesia recorded zero cases from December 2019 to February 2020, when China was severely affected by the novel coronavirus/SARS-CoV-2. On March 2, 2020, President Joko Widodo announced Indonesia's initial two COVID-19 infections. Given that Indonesia has the fourth-highest population in the world, more hardship is anticipated there than in other, less crowded nations.[2]

The severe impact of COVID-19 in the past two years has resulted in global efforts to build herd immunity, starting from the individual level and reaching the population level.[3] Referring to national data, a total of 202,623,385 people (97%) have received the first dose of vaccine, while a total of 170,201,649 people (81%) have received the second dose, and a total of 56,829,093 people (24%) have received the third dose (updated on August 4, 2022). At least 70–85% of the population must receive vaccinations in order to acquire herd immunity. Public perceptions change along with the changing condition of the pandemic.[4]

There is currently no licensed coronavirus vaccine for human use. Therefore, the rapid research and development cycle and the scant post-vaccination monitoring raise significant public concerns regarding the safety of the COVID-19 vaccine candidate, particularly for the new platform of RNA vaccines. A common defence for not having the immunization is that there are "concerns regarding the safety of the vaccine in development" and "potential harmful effects". Since the widespread use of vaccination, adverse events following immunization (AEFI), particularly the rare ones, have increased.[5] The AEFI should be monitored for at least

four reasons, according to the Indonesian Society of Internal Medicine (PAPDI). First of all, no vaccine is completely risk-free and safe. Second, it is critical to understand the dangers and how to manage them as they manifest. Third, to preserve public confidence in the immunization program, it is crucial to notify the public about AEFIs appropriately. Lastly, monitoring AEFIs contributes to better service quality.[6]

In consideration of the COVID-19 history, certain unfriendly public impressions surrounding the vaccine's side effects, the low level of AEFI reports, and limited scientific evidence of AEFI in Indonesia, based on the severity of AEFIs at Universitas Indonesia Hospital, researchers were motivated to conduct this study to discover the potential risks that might influence the vaccine's efficacy.

## METHODS

This observational study assessed the effectiveness of *Pfizer* and *Sinovac* vaccines using a non-experimental, descriptive, cross-sectional study design. Research participants who received vaccinations at Universitas Indonesia Hospital were directly interviewed to gather data prospectively. Besides, this study used online forms to collect the required information from participants. The information was then categorized, and monitoring was done for 28 days. This research was conducted at the Universitas Indonesia Hospital in August to September 2022.

Data monitoring was carried out successively based on the following timeline. The timeline for monitoring AEFI events was performed in the first 15 minutes of observation at the hospital, 15 minutes to 24 hours, 24 to 48 hours, 48 hours to 7 days and the next 7 to 28 days, respectively. A Google Form in Bahasa was created with a 5-minute completion time for the questionnaire to evaluate AEFI. Therefore, according to the timeframe for the research at the Universitas Indonesia Hospital, the questionnaire covered an AEFI evaluation with five steps.

Participants completed a survey in the Google Form containing information about their personal identity, medical conditions, and perceived AEFI complaints. According to the timeline, the questionnaire data was collected in five stages. Personal data in the questionnaire covered name, gender, telephone number, date of birth, weight and height, blood type, occupation, the previous dose of vaccine, and the dose received during vaccination at the Universitas Indonesia Hospital during recruitment. The questionnaire's medical information also included comorbidities, allergy and COVID-19 histories, hospitalizations in the last three months, and drug use in the previous six months. The questionnaire had closed-ended inquiries concerning AEFI matters. The questionnaire sheet used in the survey is shown in the Supplementary Data 3. The information from the questionnaire was entered into a Microsoft Excel sheet and statistically examined using SPSS 25 and Microsoft Excel. The incidence of AEFI was compared with gender, age, BMI, comorbidities, vaccine types, history of allergies, prior COVID-19, history of hospital admission in the previous three months, and history of medication in the last six months using the Chi-square test. The significance level ($P$=0.05) was applied to perform statistical comparisons.

The Universitas Indonesia Hospital Ethics Committee had accepted this study under approval number S-033/KETLIT/RSUI/VIII/2022 with protocol number 2022-07-165.

## RESULTS

In total, 272 participants were surveyed to obtain a minimum sample of 137 participants. However, only 261 subjects agreed to participate in the study by completing the given online form and meeting the inclusion and exclusion criteria. Of the total of 261 participants, the mean age was 29.88±10.86 years (mean±standard deviation (SD)). The participants consisted of 148 females (57%) and 113 males (43%). The average body mass index (BMI) was 22.9±0.86, with the highest BMI category of underweight - normal (<18.5–24.9) with a total of 187 participants (72%).

Two groups were formed from the participants. The first group had 149 people (57%) who received

the *Pfizer* (BNT162b2) vaccination, while the second group had 112 individuals (43%) who received the *Sinovac* vaccine. Only 31 participants (12%) had comorbidities and 54 participants (21%) took medication in the last 6 months. A total of 13 participants (5%) experienced a hospitalization within the past three months. Meanwhile, participants who had a history of allergies and COVID-19 were 31 participants (12%) and 81 participants (31%), respectively. Table 1 describes the specific participant characteristics in detail.

Overall, the AEFI was divided into 4 monitoring period, namely the initial 15 minutes during hospital observation, 15 minutes to 24 hours, 24 hours to 48 hours, and 48 hours to 7 days. In the initial 15 minutes, a total of 197 participants (75%) experienced AEFI.

Table 1. Characteristics of the Participants

| Variable | Category | Frequency | Percentage |
|---|---|---|---|
| Age | Mean±SD | 29.88±10.86 | |
| | Adolescence aged ≤25 years | 116 | 44% |
| | Adulthood aged 26-45 years | 109 | 42% |
| | Elderly aged >45 years | 36 | 14% |
| Gender | Female | 148 | 57% |
| | Male | 113 | 43% |
| Body Mass Index (BMI) | Mean±SD | 22.9±0.86 | |
| | Underweight - Normal (<18.5 to 24.9) | 187 | 72% |
| | Overweight - Obese (25 to ≥27) | 74 | 28% |
| Vaccine types | BNT162b2 (*Pfizer)* | 149 | 57% |
| | *Sinovac* | 112 | 43% |
| Vaccine variation | *Pfizer* | 8 | 3% |
| | *Pfizer* + *Pfizer* | 14 | 5% |
| | *Sinovac* + *Sinovac* | 11 | 4% |
| | *Sinovac* + *Sinovac* + *Sinovac* | 91 | 35% |
| | *Sinovac* + *Sinovac* + *Pfizer* | 23 | 9% |
| | *Pfizer* + *Pfizer* + *Pfizer* | 23 | 9% |
| | *Astrazeneca* + *Astrazeneca* + *Pfizer* | 19 | 7% |
| | *Moderna* + *Moderna* + *Pfizer* | 8 | 3% |
| | *Sinovac* + *Sinovac* + *Sinovac* + *Sinovac* | 10 | 4% |
| | *Sinovac* + *Sinovac* + *Pfizer* + *Pfizer* | 14 | 5% |
| | *Sinovac* + *Sinovac* + *Moderna* + *Pfizer* | 34 | 13% |
| | *Astrazeneca* + *Astrazeneca* + *Pfizer* + *Pfizer* | 6 | 2% |
| Dose | 1st dose *Pfizer* | 8 | 3% |
| | 2nd dose *Pfizer* | 14 | 43% |
| | 3rd dose *Pfizer* | 73 | 28% |
| | 4th dose *Pfizer* | 54 | 43% |
| | 2nd dose *Sinovac* | 11 | 43% |
| | 3rd dose *Sinovac* | 91 | 35% |
| | 4th dose *Sinovac* | 10 | 43% |
| Comorbidity | No | 230 | 88% |
| | Yes | 31 | 12% |
| History of allergy | No | 229 | 88% |
| | Food allergy | 28 | 11% |
| | Drug allergy | 4 | 2% |
| Hospitalization in the last 3 months | No | 248 | 95% |
| | Yes | 13 | 5% |
| History of medication in the last 6 months | No | 207 | 79% |
| | Yes | 54 | 21% |
| History of COVID-19 | No | 180 | 69% |
| | Yes | 81 | 31% |

Table 2. AEFIs and the severity levels in the initial 15 minutes observation at the hospital and in 15 minutes to 24 hours

| AEFI | 15 minutes | | | | 15 minutes – 24 hours | | | |
|---|---|---|---|---|---|---|---|---|
| | Mild | Moderate | Severe | PLT | Mild | Moderate | Severe | PLT |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Local Adverse Events | | | | | | | | |
| Pain at the injection site | 103 (39.5) | 24 (9.2) | 0 (0.0) | 0 (0.0) | 134 (51.3) | 25 (10.0) | 0 (0.0) | 0 (0.0) |
| Redness/erythema | 4 (1.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 17 (6.5) | 2 (1.0) | 0 (0.0) | 0 (0.0) |
| Swelling/induration | 19 (7.3) | 2 (0.8) | 1 (0.4) | 0 (0.0) | 24 (9.2) | 6 (2.0) | 1 (0.4) | 0 (0.0) |
| Itching/pruritus associated with injection | 6 (2.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 17 (6.5) | 1 (0.4) | 0 (0.0) | 0 (0.0) |
| Systemic Adverse Events | | | | | | | | |
| Pain in the legs | 24 (9.2) | 4 (1.5) | 0 (0.0) | 0 (0.0) | 34 (13.0) | 5 (1.9) | 0 (0.0) | 0 (0.0) |
| Fever | 36 (13.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 43 (16.5) | 2 (0.8) | 0 (0.0) | 0 (0.0) |
| Nausea/vomiting | 4 (1.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (3.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Headache | 31 (11.9) | 8 (3.1) | 1 (0.4) | 0 (0.0) | 37 (14.2) | 8 (3.1) | 1 (0.4) | 0 (0.0) |
| Fatigue | 70 (26.8) | 27 (10.3) | 1 (0.4) | 0 (0.0) | 91 (34.9) | 28 (10.7) | 1 (0.4) | 0 (0.0) |
| Myalgia | 44 (16.9) | 15 (5.7) | 0 (0.0) | 0 (0.0) | 54 (20.7) | 18 (6.9) | 0 (0.0) | 0 (0.0) |
| Acute allergic reaction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Rash | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Joint pain | 34 (13.0) | 14 (5.4) | 1 (0.4) | 0 (0.0) | 54 (20.7) | 17 (6.5) | 3 (1.1) | 0 (0.0) |
| Other adverse event | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Note: PLT=*Potentially Life-Threatening*

Table 3. AEFIs and the severity levels at 24 to 48 hours and 48 hours to 7 days

| AEFI | 24 to 48 hours | | | | 48 hours to 7 days | | | |
|---|---|---|---|---|---|---|---|---|
| | Mild | Moderate | Severe | PLT | Mild | Moderate | Severe | PLT |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Local Adverse Events | | | | | | | | |
| Pain at the injection site | 72 (27.6) | 3 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Redness/erythema | 7 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Swelling/induration | 13 (5.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Itching/pruritus associated with injection | 9 (3.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) |
| Systemic Adverse Events | | | | | | | | (0.0) |
| Pain in the legs | 16 (6.1) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 7 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fever | 26 (10.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (3.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nausea/vomiting | 4 (1.5) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 2 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Headache | 32 (12.3) | 5 (1.9) | 0 (0.0) | 0 (0.0) | 16 (6.1) | 4 (1.5) | 0 (0.0) | 0 (0.0) |
| Fatigue | 49 (18.8) | 10 (3.8) | 1 (0.4) | 0 (0.0) | 16 (6.1) | 2 (0.8) | 1 (0.4) | 0 (0.0) |
| Myalgia | 36 (13.8) | 3 (1.1) | 0 (0.0) | 0 (0.0) | 15 (5.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Acute allergic reaction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Rash | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 90.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Joint pain | 31 (11.9) | 4 (1.5) | 0 (0.0) | 0 (0.0) | 16 (6.1) | 1 (0.4) | 0 (0.0) | 0 (0.0) |
| Other adverse event | 3 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Note: PLT=*Potentially Life-Threatening*

Then, in the 15 minutes to 24 hours of monitoring, a total of 215 participants (82%) experienced an increase in AEFI from the previous monitoring. In the 24 to 48 hours monitoring and 48 hours to 7 days monitoring, the incidence of AEFI decreased to 133 participants (50%) and 57 participants (21%).

Table 2 shows that in the initial 15 minutes after vaccination, participants reported 3 main complaints: 130 participants (39.5%) experienced pain at the injection site, 70 (26.8%) experienced fatigue, and 44 (16.9%) participants experienced myalgia with mild severity based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials issued by the Food and Drug Administration.

At moderate severity in the initial 15 minutes, the main complaint felt by participants was fatigue in 27 participants (10.3%), followed by pain at the injection site and myalgia. At severe severity in the initial 15 minutes, there was 1 participant in each AEFI category, namely swelling/induration, headache, fatigue and joint pain. At 15 minutes to 24 hours of monitoring (Table 2), there was an increase

in the incidence of AEFI with mild severity, where 134 participants (51.3%) experienced pain at the injection site, 91 participants (34.9%) experienced fatigue, and 20.7% of the participants experiencing myalgia and joint pain.

Table 3 shows the incidence of AEFI at 24 hours to 48 hours and 48 hours to 7 days of monitoring. In 24 to 48 hours of monitoring, there was a decrease in the incidence of AEFI from 134 participants (51.3%) to 72 participants (27.6%) experiencing pain at the injection site. Then, the number of participants experiencing fatigue of mild severity decreased from 91 participants (34.9%) to 49 participants (18.8%). At moderate severity, there was also a decrease from 28 participants (10.7%) to 10 participants (3.8%). On monitoring for 48 hours to 7 days (Table 3), there was no longer any AEFI at the injection site. The most common complaints during 48 hours to 7 days monitoring were headache, fatigue and joint pain. The detailed information is presented in the following table.

Table 4 shows that, with a $P<0.05$, the incidence of AEFI in the first 15 minutes was affected by gender, BMI, vaccine types, comorbidities, history of allergic reactions, taking medication during the previous 6 months, and a prior COVID-19 infection. Meanwhile, monitoring from 15 minutes to 24 hours revealed that the risk factors of gender, vaccine types, comorbidities, history of allergic reactions, taking medication in the previous 6 months, and prior COVID-19 infection all had a $P<0.05$ on the incidence of AEFI.

The incidence of AEFI was affected by gender, age, vaccine types, history of allergic reactions, and previous COVID-19 infection in the 24 to 48 hours monitoring ($P<0.05$), as shown in Table 5.

Table 4. Risk factors affecting AEFI in the initial 15 minutes and 15 minutes to 24 hours

| Risk factor | AEFI in 15 minutes | | | | AEFI in 15 minutes to 24 hours | | | |
|---|---|---|---|---|---|---|---|---|
| | No AEFI n (%) | AEFI n (%) | *P* | OR (95% CI) | No AEFI n (%) | AEFI n (%) | *P* | OR (95% CI) |
| Gender | | | | | | | | |
| Female | 27 (18.2) | 121 (81.8) | 0.009 | 0.458 (0.258-0.813) | 16 (10.8) | 132 (89.2) | 0.002 | 0.335 (0.172-0.653) |
| Male | 37 (32.7) | 76 (67.3) | | | 30 (26.5) | 83 (73.5) | | |
| Age | | | | | | | | |
| ≤25 years | 27 (23.3) | 89 (76.7) | 0.215 | - | 20 (17.2) | 96 (82.8) | 0.071 | - |
| 26–45 years | 24 (22.0) | 85 (78.0) | | | 15 (13.8) | 94 (86.2) | | |
| >45 years | 13 (36.1) | 23 (63.9) | | | 11 (30.6) | 25 (69.4) | | |
| Body Mass index (BMI) | | | | | | | | |
| Underweight-normal (<18.5 to 24.9) | 35 (18.7) | 152 (81.3) | 0.001 | 0.357 (0.197-0.647) | 29 (15.5) | 158 (85.5) | 0.155 | 0.615 (0.315-1.204) |
| Overweight - obese (25 to ≥27) | 29 (39.2) | 45 (60.8) | | | 17 (23.0) | 57 (77.0) | | |
| Vaccine type | | | | | | | | |
| *Pfizer* | 24 (16.1) | 125 (83.9) | <0.001 | 2.894 (1.615-5.185) | 15 (10.1) | 134 (89.9) | <0.001 | 3.419 (1.74-6.717) |
| *Sinovac* | 40 (35.7) | 72 (64.3) | | | 31 (27.7) | 81 (72.3) | | |
| Comorbidities | | | | | | | | |
| No | 62 (27) | 168 (73) | 0.013 | 5.351 (1.24-23.093) | 45 (19.6) | 185 (80.4) | 0.023 | 7.297 (0.969-54.945) |
| Yes | 2 (6.5) | 29 (93.5) | | | 1 (3.2) | 30 (96.8) | | |
| History of allergic reactions | | | | | | | | |
| No | 62 (27.1) | 167 (72.9) | 0.008 | 5.569 (1.292-23.997) | 45 (19.7) | 184 (80.3) | 0.023 | 7.582 (1.008-57.028) |
| Yes | 2 (6.3) | 30 (93.8) | | | 1 (3.1) | 31 (96.9) | | |
| Acute infection/hospitalization in the last 3 months | | | | | | | | |
| No | 62 (25) | 186 (75) | 0.741 | 1.833 (0.395-8.499) | 45 (18.1) | 203 (81.9) | 0.476 | 2.66 (0.337-20.984) |
| Yes | 2 (15.4) | 11 (84.6) | | | 1 (7.7) | 12 (92.3) | | |
| History of medication in the last 6 months | | | | | | | | |
| No | 58 (28) | 149 (72) | 0.012 | 3.114 (1.264-7.669) | 43 (20.8) | 164 (79.2) | 0.008 | 4.457 (1.327-14.975) |
| Yes | 6 (11.1) | 48 (88.9) | | | 3 (5.6) | 51 (94.4) | | |
| History of COVID-19 | | | | | | | | |
| No | 54 (30) | 126 (70) | 0.002 | 3.043 (1.459-6.344) | 38 (21.1) | 142 (78.9) | 0.034 | 2.442 (1.083-5.506) |
| Yes | 10 (12.3) | 71 (87.7) | | | 8 (9.9) | 73 (90.1) | | |

Note: $P<0.05$

Table 5. Risk factors affecting AEFI in 24 to 48 hours and in 48 hours to 7 days

| Risk factor | AEFI in 24 to 48 hours | | | | AEFI in 48 hours to 7 days | | | |
|---|---|---|---|---|---|---|---|---|
| | No AEFI n (%) | AEFI n (%) | *P* | OR (95% CI) | No AEFI n (%) | AEFI n (%) | *P* | OR (95% CI) |
| Gender | | | | | | | | |
| Female | 57 (38.5) | 91 (61.5) | <0.001 | 0.371 (0.224-0.614) | 109 (73.6) | 39 (26.4) | 0.05 | 0.53 (0.284-0.987) |
| Male | 71 (62.8) | 42 (37.2) | | | 95 (84.1) | 18 (15.9) | | |
| Age | | | | | | | | |
| ≤25 years | 56 (48.3) | 60 (51.7) | | | 101 (87.1) | 15 (12.9) | | |
| 26–45 years | 47 (43.1) | 62 (56.9) | 0.023 | - | 76 (69.7) | 33 (30.3) | 0.006 | - |
| >45 years | 25 (69.4) | 11 (30.6) | | | 27 (75.0) | 9 (25.0) | | |
| Body Mass index (BMI) | | | | | | | | |
| Underweight - Normal (<18.5 to 24.9) | 87 (46.5) | 100 (53.5) | 0.218 | 0.7 (0.408-1.203) | 143 (76.5) | 44 (23.5) | 0.323 | 0.693 (0.348-1.377) |
| Overweight - Obese (25 to ≥27) | 41 (55.4) | 33 (44.6) | | | 61 (82.4) | 13 (17.6) | | |
| Vaccine type | | | | | | | | |
| *Pfizer* | 67 (59.8) | 45 (40.2) | 0.003 | 2.148 (1.304-3.539) | 107 (71.8) | 42 (28.2) | 0.004 | 2.538 (1.325-4.864) |
| *Sinovac* | 61 (40.9) | 88 (59.1) | | | 97 (86.6) | 15 (13.4) | | |
| Comorbidities | | | | | | | | |
| No | 118 (51.3) | 112 (48.7) | 0.056 | 2.213 (0.998-4.905) | 187 (81.3) | 43 (18.7) | 0.002 | 3.581 (1.64-7.822) |
| Yes | 10 (32.3) | 21 (67.7) | | | 17 (54.8) | 14 (45.2) | | |
| History of allergic reactions | | | | | | | | |
| No | 118 (51.5) | 111 (48.5) | 0.038 | 2.339 (1.06-5.159) | 184 (80.3) | 45 (19.7) | 0.037 | 2.453 (1.117-5.386) |
| Yes | 10 (31.3) | 22 (68.8) | | | 20 (62.5) | 12 (37.5) | | |
| Acute infection/hospitalization in the last 3 months | | | | | | | | |
| No | 125 (50.4) | 123 (49.6) | 0.085 | 3.388 (0.91-12.605) | 197 (79.4) | 51 (20.6) | 0.041 | 3.311 (1.066-10.281) |
| Yes | 3 (23.1) | 10 (76.9) | | | 7 (53.8) | 6 (46.2) | | |
| History of medication in the last 6 months | | | | | | | | |
| No | 106 (51.2) | 101 (48.8) | 0.221 | 1.527 (0.832-2.802) | 166 (80.2) | 41 (19.8) | 0.139 | 1.705 (0.866-3.354) |
| Yes | 22 (40.7) | 32 (59.3) | | | 38 (70.4) | 16 (29.6) | | |
| History of COVID-19 | | | | | | | | |
| No | 96 (53.3) | 84 (46.7) | 0.045 | 1.75 (1.027-2.982) | 142 (78.9) | 38 (21.1) | 0.746 | 1.145 (0.612-2.142) |
| Yes | 32 (39.5) | 49 (60.5) | | | 62 (76.5) | 19 (23.5) | | |

Note: *P*<0.05

Monitoring of AEFIs at 48 hours to 7 days (Tabel 5) pointed out that the incidence of AEFI was affected by age, vaccine types, comorbidities, history of allergic reactions, and hospitalization in the previous 3 months with a *P*<0.050.

Table 6 shows the relationship between the vaccine combination variations received by participants and the level of AEFIs. In the first 15 minutes, the combinations with the highest percentage of AEFIs were *Moderna* + *Moderna* + *Pfizer*, *Sinovac* + *Sinovac* + *Pfizer* + *Pfizer*, and *Astrazeneca* + *Astrazeneca* + *Pfizer* + *Pfizer*, in which 100% of participants experienced at least 1 type of AEFIs in the 15 minutes of monitoring. Meanwhile, at 15 minutes to 24 hours monitoring, the highest incidence of AEFI was observed in the combination of the *Astrazeneca* + *Astrazeneca* + *Pfizer* + *Pfizer* vaccines, in which 100% of the participants experienced AEFIs, followed by the combination of *Sinovac* + *Sinovac* + *Moderna* + *Pfizer*, where the AEFI percentage increased from 82% to 94%, and the combination of *Sinovac* + *Sinovac* + *Pfizer* + *Pfizer*, which decreased from 100% to 93% participants with at least 1 type of AEFI.

The combination of *Sinovac* + *Sinovac* vaccine had the highest AEFI incidence in 24 to 48 hours of monitoring, with 91% of participants experiencing AEFIs. This combination of *Sinovac* + *Sinovac* vaccine was higher than other combinations, followed by *Moderna* + *Moderna* + *Pfizer* and *Sinovac* + *Sinovac* + *Pfizer*, with 75% and 74% participants, respectively. In 48 hours to 7 days of monitoring, all vaccine combinations had decreased AEFIs. Of all combinations, only *Moderna* + *Moderna* + *Pfizer* had an AEFI level higher than 50%, with 75% of participants experiencing at least one type of AEFI.

Table 6. Vaccine combination variations on the incidence of AEFI

| Vaccine combination variations | AEFI in 15 minutes | | AEFI in 15 minutes to 24 hours | | AEFI in 24 to 48 hours | | AEFI in 48 hours to 7 days | |
|---|---|---|---|---|---|---|---|---|
| | No | Yes | No | Yes | No | Yes | No | Yes |
| *Pfizer* | 25% | 75% | 13% | 88% | 63% | 38% | 75% | 25% |
| *Pfizer + Pfizer* | 7% | 93% | 14% | 86% | 43% | 57% | 79% | 21% |
| *Sinovac + Sinovac* | 18% | 82% | 9% | 91% | 9% | 91% | 73% | 27% |
| *Sinovac + Sinovac + Sinovac* | 38% | 62% | 31% | 69% | 68% | 32% | 89% | 11% |
| *Sinovac + Sinovac + Pfizer* | 30% | 70% | 13% | 87% | 26% | 74% | 78% | 22% |
| *Pfizer + Pfizer + Pfizer* | 22% | 78% | 13% | 87% | 35% | 65% | 65% | 35% |
| *Astrazeneca + Astrazeneca + Pfizer* | 16% | 84% | 11% | 89% | 42% | 58% | 74% | 26% |
| *Moderna + Moderna + Pfizer* | 0% | 100% | 13% | 88% | 25% | 75% | 25% | 75% |
| *Sinovac + Sinovac + Sinovac + Sinovac* | 30% | 70% | 20% | 80% | 40% | 60% | 80% | 20% |
| *Sinovac + Sinovac + Pfizer + Pfizer* | 0% | 100% | 7% | 93% | 36% | 64% | 57% | 43% |
| *Sinovac + Sinovac + Moderna + Pfizer* | 18% | 82% | 6% | 94% | 50% | 50% | 79% | 21% |
| *Astrazeneca + Astrazeneca + Pfizer + Pfizer* | 0% | 100% | 0% | 100% | 67% | 33% | 100% | 0% |

In dealing with AEFI events, some participants used at least one type of therapy. In the 15 minutes of monitoring, 25 participants used therapy to relieve AEFI. The number of participants who used therapy increased in 4 participants in the 15 minutes to 24 hours monitoring. Meanwhile, at 24 to 48 hours of monitoring and 48 hours to 7 days of monitoring, the participants who used therapy decreased by 3 at each monitoring time.

## DISCUSSION

In this study, the highest level of AEFI was found in 15 minutes to 24 hours of monitoring, in which 215 participants (82%) experienced AEFI. This number increased from the previous monitoring, with 197 (75%) participants experiencing AEFI. Then, with 133 participants (50%), it decreased within 24 to 48 hours of monitoring. In the 48 hours to 7 days of monitoring, the decline in AEFI was very large, with 57 participants (21%) experiencing AEFI. This incident is in line with Mohsin et al, who reported an average of only 1–3 days of adverse events, and the study did not identify any examples of serious effects or hospitalizations.[7] Moreover, Lai et al compared AEFI in *CoronaVac* and *Comirnaty* vaccines and stated that the proportion of AEFI reached its peak on the first day after vaccination and gradually decreased.[8]

In this study, 130 participants (39.5%) reported discomfort at the injection site, the highest prevalence of AEFI symptoms in the first 15 minutes after immunization. Then, 44 individuals (16.9%) and 70 people (26.8%) reported having myalgia. Phase 3 study from the United States revealed that following the first and second doses of the mRNA-1273 vaccination, systemic and injection site-related adverse events occurred more frequently in the mRNA-1273 vaccine group than in the placebo group. Additionally, soreness at the injection site is the most prevalent adverse event connected to the site of injection, which is similar with previous research by Bostan et al, in which a local injection site response was the most often observed side effect.[9]

In this study, the perceived severity of AEFI was dominated by mild severity, while moderate, severe, and potentially life-threatening events occurred in a few cases only. This is consistent with the findings of Bostan et al. They found that the modest, self-limiting responses to the *Sinovac-CoronaVac* and *Pfizer-BioNTech* COVID-19 vaccines were both systemic and local. No study participants had severe or life-threatening systemic or local side effects that would have stopped them from getting subsequent vaccines.[9]

The findings of this study are also in line with those of Aryal et al, who found that the most common local reaction was pain at the injection site and rarely swelling, while the most common systemic reactions were lethargy, headache, and muscle pain. These results align with preliminary safety data analyses carried out in China, Bahrain, Egypt, Jordan, and the United Arab Emirates, which found that injection site pain, rash, swelling, induration, and itching were the most frequently reported local reactions. At the same

time, headache, fever, myalgia, fatigue, arthralgia, cough, dyspnea, nausea, and diarrhea were the most frequently reported systemic reactions.[10] Global side effects following COVID-19 vaccination varied by vaccine type, according to study by Anjorin et al. However, the most frequently reported symptoms were fatigue, headache, muscle and joint pain, allergic skin reactions, and chills. The most common symptoms that appeared several days after vaccination were light fever, fever, and pain or redness at the injection site.[11]

Different demographic profiles had been investigated in this study and were associated with existing AEFIs.The age category was divided into three groups in this study. The level of AEFI complaints was dominated by the age group of 17-35 years, followed by 45 years and over. According to Le et al, participants between the ages of 18 and 55 were more likely than participants over 55 to suffer AEFI. Persons between 18 and 55 years old were 1.9 times more likely than participants over 55 to develop AEFIs.[12]

Moreover, this study is also in line with Parida et al, who obtained that the majority of AEFIs were mild. The most frequent AEFI was pain at the injection site, followed by fever and myalgia. Younger people reported AEFIs more frequently than elders. Participants aged 18–29 years (younger) reached 34.6%, while in South India, it was 48.4%, and most AEFIs were reported among the younger age group.[13] In comparison to the elder demographic, Ripabelli noted that 70% of young persons aged 55 experienced adverse effects. In addition to having a stronger immune system than older people, older people have a reduced capacity to respond effectively to vaccination, as evidenced by a lower frequency of neutralizing antibodies following the *Comirnaty* vaccination.[14]

In this study, the percentage of AEFI incidence was higher in female participants than in male participants. In the 15 minutes of monitoring, the AEFI in female participants was significantly higher ($P$=0.009) compared to that in males. It also occured in the 15 minutes to 24-hours of monitoring ($P$=0.002), 24to 48 hours of monitoring, and 48 hours to 7 days of monitoring, which significantly differed ($P$<0.001 and $P$=0.050, respectively). This is in line with findings from Ripabelli et al, which stated that most female vaccine recipients reported adverse events, with a twofold increase in the likelihood of reporting reactions compared to men. There might be gender-specific variations in vaccine side effects. Studies on different vaccines showed that the cellular immune response in men was generally suppressed compared to women. The significant biological link between sex and immunological response and its implications on disease susceptibility, transmission, and vaccination outcome can be used to explain this discrepancy. The primary sex hormones appear to oppose the innate and adaptive immune systems; for example, rising estradiol and testosterone levels reduce the antibody responses elicited by vaccination.[15]

Additionally, behavioural attitudes toward reporting side effects and autoimmune illnesses were recorded more commonly in women than men. Finally, women are more likely to have side effects due to their higher body fat percentage, which influences the drug's volume of distribution and clearance rate.[14] Chakraborty et al found that the number of women with AEFI was higher than that of men for both local and systemic reactions.[15] Parida et al also demonstrated that, with statistically significant differences ($P$=0.010), AEFI was 1.30 times more common in women than in men.[13]

Body Mass Index (BMI) does not significantly affected the level of AEFI in this study. Only in the 15 minutes of monitoring, the AEFI in Underweight - Normal (<18,5 to 24,9) participants was significantly higher ($P$=0.001) compared to that in Overweight - Obese (25 to ≥27), but the percentage of participants in the normal weight category (≥18.5 to <24.9) was higher than those in the overweight and obese categories. This supports the finding by Hidayat et al that those with BMIs below 25 kg/m$^2$ (underweight or normoweight) were more likely to have AEFIs than those with BMIs above 25 kg/m$^2$ (overweight).[16] Iguacel et al discovered that people in the underweight and normal weight groups had a higher likelihood of experiencing COVID-19 adverse effects

(fever, vomiting, diarrhea, and chills) than people who were overweight (including obese).[17]

In this study, the *Pfizer* vaccine had a higher AEFI percentage than the *Sinovac* vaccine. In the first 15 minutes and in 15 minutes to 24 hours, the AEFI percentage of *Pfizer* was significantly (*P*<0.001) higher than the *Sinovac* vaccine. In 24 to 48 hours of monitoring, *Pfizer* showed significantly higher AEFIs than *Sinovac* (*P*=0.003), and so did *Pfizer* in 48 hours to 7 days of monitoring (*P*=0.004). This is similar with Bostan et al who noted that the *Pfizer-BioNTech* vaccine in the first and second doses had a statistically higher rate of systemic and local side effects than the *Sinovac-CoronaVac* vaccine.[9]

Additionally, Chen et al noticed that the incidence of AEFI was 23.0% (95% CI=20.0-26.0%; $I^2$= 55.71%), 48.0% (95% CI=28.0-84.0%; $I^2$=99.99%), and 76.0% (95% CI=69.0-84.0%; $I^2$=84.46%), respectively, among inactivated vaccines, mRNA-based vaccines, and viral vector vaccines.[18] *Pfizer-BioNTech* recipients demonstrated a 5.37-fold (95% CI=2.57-11.22) higher likelihood of side effects than *Sinopharm* recipients, according to Mohsin et al.[7] The related claim that *CoronaVac* had less reactogenicity than *Comirnaty* was supported by Lai et al They also stated that those who received *CoronaVac* as opposed to *Comirnaty* had a considerably decreased probability of adverse reactions (global, local, and systemic) two weeks after immunization.[8]

Comorbidity had a big impact on AEFI level in this study. According to Parida et al, people with comorbidities were 2.08 times more likely than healthy individuals to suffer AEFI (*P*<0.001).[13] A history of COVID-19 infection and allergies greatly impacts AEFI levels. This is consistent with the findings by Parida et al, who revealed that AEFI symptoms and a history of allergies were strongly correlated.[13]

Based on studies by Juliane et al, multivariate analysis in this study identified co-morbidities, including chronic lung disease, chronic kidney disease, and cardiovascular disease, that had a substantial association with a high risk of mortality. According to multiple research studies, COVID-19 patients with chronic comorbidities had an increased risk of COVID-19 events, including death. Similar to the relationship with AEFI events, comorbidities increase the incidence of AEFI in patients.[19] Significant predictors of AEFI, in addition to gender, were comorbidities, a history of using corticosteroids, a history of allergies, a history of using drugs within the previous six months, and a history of being hospitalized within the previous three months.[13] Additionally, the history of medication use over the previous six months greatly impacts AEFIs.

The level of AEFI is greatly impacted by COVID-19 history. This is consistent with Ossato et al, who found that previously immunized individuals with COVID-19 infection had a considerably greater antibody response following a single vaccination döşe.[20] All 18 COVID-19 patients who had previously been diagnosed had mild reactions, and nine of them reported moderate reactions, which were connected to a history of SARS-CoV-2 infection, according to Ripabelli et al. This correlation may be explained by increased immunogenicity in those who have had an infection and have antibodies against healthy individuals, as well as heightened concern about side effects, even in those who only have minor symptoms.[14]

Based on the different combinations, the *Pfizer* vaccine combination had a higher AEFI than the *Sinovac* vaccine. During the initial 15 minutes of monitoring and the next 24 to 48 hours of monitoring, the second dosage of the *Pfizer* vaccine in this trial showed a larger AEFI than the first dose. This is consistent with the FDA analysis, which found that after the second dosage of the vaccine, local adverse effects were slightly more common than they were after the first dose.[21]

This is in line with finding by Ripabelli, which obtained that about 80% of people who participated in active surveillance disclosed at least one AEFI after the first or second dose. Additionally, it is consistent with earlier national studies for mRNA-based vaccinations, highlighting the lack of a significant difference between the two dosages. However, as seen elsewhere, some reactions commonly happened after the second dose.[14] The

investigation by Maruyama et al into the *Pfizer* vaccine related to AEFI discovered that the incidence of systemic reactions increased following the second dose, which was consistent with the results of the earlier study.[22] In contrast, it could not further examine which vaccination combination substantially impacted the occurrence of AEFI due to the less widespread distribution of the vaccine variety.

In this research, some participants who experienced AEFIs took medication independently. The most commonly consumed drug by participants to relieve AEFI symptoms was Paracetamol. This is consistent with Ripabelli et al, who reported that 141 participants (50.2%) had adverse effects after receiving *Pfizer*'s second dose (n=281). These participants were treated for their symptoms mostly with paracetamol (n=101; 71.6%), followed by NSAIDs (n=21; 14.9%).[14] According to Mohsin et al, more than 70% of responders who had *Pfizer* and *Moderna* vaccine adverse effects took medicine. On the other hand, only 9.87% of individuals took medication and had side effects after getting *Sinopharm* vaccinations.[7]

## LIMITATION

This study has some limitations. Following the vaccination, we only conducted a one-week follow-up. To evaluate late symptoms of immunization, long-term follow-up is required. Despite the fact that a high quality of data was acquired due to the target population's degree of knowledge and skills about health concerns and their ability to recognize post-vaccination symptoms, the use of self-reported data might potentially create misclassification bias. Additionally, we did not conduct immunological testing to demonstrate the respondents' immune responses.

## CONCLUSION

This study revealed that *Pfizer* and *Sinovac* COVID-19 vaccines were safe to administer as AEFIs were mostly mild and automatically disappeared and decreased after 1 to 3 days. This research offered a thorough analysis of the variables influencing AEFIs in immunization participants at the Universitas Indonesia Hospital. The findings of this study demonstrated that female participants with comorbidities, prior allergy history, history of medication use during the past six months, and history of COVID-19 had a higher risk of AEFI and a statistically significant effect ($P$ <0.005). Furthermore, people receiving mRNA immunization should be monitored more closely than those receiving inactivated vaccines because the *Pfizer* vaccine significantly worsened side effects compared to the *Sinovac* vaccine.

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## CONFLICT OF INTEREST

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