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Risk of adverse events following CoronaVac's COVID-19 vaccination in women with and without autoimmunity

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ABSTRACT

Introduction: Adverse Events Following Immunization (AEFI) of the COVID-19 vaccine is one of the important considerations, especially in patients with autoimmunity. This study aims to compare the number of CoronaVac AEFIs in women with and without autoimmunity.

Methodology: This is a retrospective cohort study with an unpaired comparative analytic design with a retrospective cohort method. We recruited 602 volunteers, 182 women with autoimmunity and 420 without autoimmunity. We included women who received the CoronaVac vaccine, aged 17–65 years. Data were analyzed using the chi-square or fisher exact method as an alternative.

Results: We found a generally increased risk for AEFI in women with autoimmunity (RR = 1.179; 95% CI 1.059–1.313; p = 0.007) compared to women without autoimmunity, especially for systemic (RR = 1.1271; 95% CI 1.045–1.545; p = 0.025), allergic (RR = 2.052; 95% CI 1.070–3.932; p = 0.045), fever (RR = 2.163 95%; CI 1.093–4.282; p = 0.039), fatigue (RR = 2.182 95%; CI 1.558–3.056; p = 0.001), and headache (RR = 1.619 95%; CI 1.164–2.251; p = 0.006). On the other hand, we found no increased risk for the overall severity of AEFI (RR = 0.851 95% CI; 0.655–1.105; p = 0.256). We also found a relapse of autoimmune condition in 10.4% (n = 19) after CoronaVac vaccination.

Conclusions: There is an increased risk of AEFI after CoronaVac vaccination in women with autoimmunity compared to those without the condition. Although the severity of AEFIs and risk of autoimmune relapse were relatively low.

1. Introduction

Vaccine administration is known to cause side effects to recipients, which are known as adverse events after immunization (AEFI). The risk and type AEFIs that arise can be different for each individual.[1] People with certain conditions, for example, people with autoimmune disorders (PWAD), have a different immune response than those without autoimmunity (PWOA).[2] The current pandemic condition requires people to receive the COVID-19 vaccine, one of which is CoronaVac.[3] CoronaVac is a traditional whole spike protein vaccine with aluminum-hydroxide adjuvant, given as a two doses primary vaccination schedule three months apart. Unfortunately, research on AEFI against CoronaVac in people with autoimmunity is rarely done due to the exclusion of most people from the COVID-19 vaccine trial.[4–8] This study aims to compare the AEFI risk of CoronaVac vaccination in PWAD compared to PWOA done in Indonesia's community setting.

2. Methodology

2.1. Patients and settings

This study was conducted with an unpaired categorical comparative analytical analysis using the retrospective cohort method. Data was collected through the COVID-19 vaccine recipients' community health center database from September to October 2021 in several provinces of Indonesia (Jakarta, Banten, and West Borneo). Vaccine recipients were recruited from the mandatory vaccination program conducted by the government of the Republic of Indonesia. The subjects' responses to the database questionnaire provided the autoimmune disease diagnosis. The study was approved by the Medical Research Ethics Committee, Faculty

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of Medicine, Universitas Pelita Harapan, Tangerang. Subjects have been given an adequate explanation and agreed to participate in the research.

2.2. Data collection and assessment

We included women who have received the CoronaVac primary vaccination program (two doses of vaccine), with an age range of 17–65 years, in the study. The data obtained in this study include gender, age, autoimmune diagnosis, COVID-19 vaccination status, and AEFI characterization (type and grade), which was collected prospectively as part of national COVID-19 vaccination safety monitoring up to 30 days after the first and second dose. We grade the severity of AEFI using Common Terminology Criteria of Adverse Events (CTCAE from NIH, 2018). The severity of AEFI was graded as follows: grade 1 (mild) are AEFIs that create a sense of uncomfortable sensation; grade 2 (moderate) are AEFIs that cause disturbing symptoms; grade 3–5 (severe) are AEFIs that cause symptoms that interfere with daily activities/needs to be treated to the one that causes death.

2.3. Statistical analysis

Analysis was done using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Chi-square analysis and its alternative (Fischer exact test) were used to determine the relationship between autoimmunity status and risk of specific AEFIs. Any p-values <0.05 were considered statistically significant.

3. Results

The community database included 602 people with autoimmunity and 3424 people without autoimmunity. After fitting with the inclusion criteria, the total volunteers included, in the final analysis, were 182 women with autoimmunity (age mean 42.84; SD 11.23) and 420 women without autoimmunity (age mean 43.21; SD 10.45), a large number of subjects were removed due to many vaccine recipients being over 65 years old at the time of the study. Detailed volunteer characteristics regarding age and autoimmune diagnosis can be seen in Table 1. The most common AEFI overall for PWADs was pain at the injection site, followed by fatigue and headache. Whereas for PWAOs, the most common AEFI overall was pain at the injection site, followed by swelling, redness, and sleepiness (Table 2). We found a recurrence of autoimmune symptoms (specific to each autoimmune diagnosis and individual patients) in 10.4% (n = 19/182) of PWADs who received CoronaVac vaccines.

We found an increased risk for overall (RR 1.179; 95% CI 1.059–1.313; p = 0.007) and specific systemic AEFIs in PWADs, especially regarding allergic reactions, fever, fatigue, and headache (Table 2). We also found an increased severity risk for allergic reactions, nausea/vomiting, heartburn/diarrhea, and headache in the PWADs group. On the other hand, there is a reduced severity risk for pain and soreness in the PWADs group compared to the PWAOs (Table 3). We did not find an increased risk for combined mild vs. moderate-severe AEFIs in PWADs compared to PWAOs (combined mild vs. moderate-severe AEFIs; RR 0.851; 95% CI 0.655–1.105; p = 0.256).

Table 1
Demographic and autoimmune diagnosis data of respondents.

Variable		PWADs		PWOAs	
		n	%	n	%
Age	17–25	25	13,7%	123	29,2%
	26–45	83	45,6%	244	58%
	46–65	74	40,6%	53	12,6%
Autoimmunity Status	Rheumatic Arthritis	67	36,8%	–	–
	Sjogren's syndrome	42	23%	–	–
	Lupus	35	19,2%	–	–
	Psoriasis/Psoriatic Arthritis	18	9,8%	–	–
	Vasculitis	16	8,7%	–	–
	Autoimmune targeting blood cells	15	8,2%	–	–
	Autoimmune targeting thyroid gland	13	7,1%	–	–
	Autoimmunity targeting nervous system	12	6,5%	–	–
	Autoimmunity targeting digestive system	10	5,4%	–	–
	Ankylosing Spondylitis	7	3,8%	–	–
	Polymyositis	5	2,7%	–	–
	Antiphospholipid Syndrome/APS	4	2,1%	–	–
	Other autoimmune disorders	16	8,7%	–	–

PWAD = people with autoimmune disorders (PWAD); PWOA = people without autoimmunity.

4. Discussion

Our study indicates an increased risk for AEFIs in women with autoimmunity compared to those without autoimmunity regarding the administration of the CoronaVac COVID-19 vaccines. Risk especially significant concerning systemic AEFIs, such as allergic reactions (RR 2.052; 95% CI 1.070–3.932; p = 0.045), fever (RR 2.163; 95% CI 1.093–4.282; p = 0.039), fatigue (RR 2.182; 95% CI 1.558–3.056; p = 0.001) and headache (RR 1.619; 95% CI 1.164–2.251; p = 0.006). These results are in line with research conducted in Brazil by Medeiros-Ribeiro et al., which showed that there was a significant relationship between

Table 2
Bivariate analysis for local vs. systemic AEFIs in PWADs compared to PWOAs.

	PWAD n = 182	PWOA n = 420	Relative Risk	*P* value
Local AEFI	112 (61.5%)	224 (53.3%)	1.153 95% CI: (0.998–1.335)	0.076
• Swelling and Redness	38 (20.9%)	119 (28.3%)	0.737 95% CI: (0.535–1.016)	0.070
• Pain	106 (58.6%)	218 (51.9%)	1.128 95% CI: (0.968–1.315)	0.158
Systemic AEFI	87 (47.8%)	158 (37.6%)	1.271 95% CI: (1.045–1.545)	0.025*
• Allergic reactions	16 (8.8%)	18 (4.3%)	2.052 95% CI: (1.070–3.932)	0.045*
• Fever (>38C)	15 (8.2%)	16 (3.8%)	2.163 95% CI: (1.093–4.282)	0.039*
• Fatigue	52 (28.6%)	55 (13.1%)	2.182 95% CI: (1.558–3.056)	0.001*
• Nauseous/vomit	16 (8.8%)	29 (6.9%)	1.273 95% CI: (0.709–2.286)	0.522
• Heartburn/ Diarrhea	15 (8.2%)	25 (6.0%)	1.385 95% CI: (0.748–2.564)	0.391
• Headache	47 (25.8%)	67 (16.0%)	1.619 95% CI: (1.164–2.251)	0.006*
• Sleepiness	22 (12.1%)	77 (18.3%)	0.659 95% CI: (0.424–1.025)	0.075
• Increase appetite	8 (4.4%)	15 (3.6%)	1.231 95% CI: (0.531–2.852)	0.800

*significant results; PWAD = people with autoimmune disorders (PWAD); PWOA = people without autoimmunity; AEFI = adverse events after immunization.

Table 3
Bivariate analysis for specific mild vs. moderate-severe AEFIs in PWADs compared to PWOAs.

		PWAD	PWOA	*Relative Risk*	*p-value*
Swelling and Redness	Mild	26 (68.4%)	83 (69.7%)	1.044 95% CI: (0.607–1.794)	1.00
	Moderate-Severe	12 (31.6%)	36 (30.3%)		
Pain and Soreness	Mild	76 (71.7%)	121 (55.5%)	0.636 95% CI: (0.454–0.891)	0.007*
	Moderate-Severe	30 (28.3%)	97 (44.5%)		
Allergic reactions	Mild	10 (62.5%)	17 (94.4%)	6.750 95% CI: (0.907–50.228)	0.035*
	Moderate-Severe	6 (37.5%)	1 (5.6%)		
Fever (>38C)	Mild	9 (60.0%)	11 (68.8%)	1.280 95% CI: (0.492–3.327)	0.894
	Moderate-Severe	6 (40.0%)	5 (31.3%)		
Fatigue	Mild	26 (50.0%)	33 (60.0%)	1.250 95% CI: (0.819–1.908)	0.398
	Moderate-Severe	26 (50.0%)	22 (40.0%)		
Nauseous/ vomit	Mild	7 (43.8%)	24 (82.8%)	3.262 95% CI: (1.317–8.080)	0.016*
	Moderate-Severe	9 (56.3%)	5 (17.2%)		
Heartburn/ Diarrhea	Mild	5 (33.3%)	18 (72.0%)	2.381 95% CI: (1.155–4.908)	0.039*
	Moderate-Severe	10 (66.7%)	7 (28.0%)		
Headache	Mild	28 (59.6%)	54 (80.6%)	2.083 95% CI: (1.145–3.792)	0.025*
	Moderate-Severe	19 (40.4%)	13 (19.4%)		

*significant results; PWAD = people with autoimmune disorders (PWAD); PWOA = people without autoimmunity; AEFI = adverse events after immunization.

autoimmunity and AEFI, especially with Systemic AEFI ($p = 0.014$). Medeiros-Ribero et al. also showed that autoimmunity did not have a significant relationship with local AEFI ($p = 0.284$).[2]

A study by Laura Boekel et al. investigated the post-vaccination AEFI of the AstraZeneca, Pfizer/BioNTech, and Moderna COVID-19 vaccine in people with and without autoimmunity. Laura Boekel et al. also showed that the most common AEFI was pain at the injection site. In contrast to our study, they found no difference in systemic AEFI between people with autoimmunity and those without autoimmunity (44% vs. 40%; RR 1.1; 95% CI 0.8–1.6; $p = 0.6$). Further analysis of their data shows that this could be caused partly by gender differences, as when they analyzed gender-based subgroups, there is an increased risk for systemic AEFIs in females (female vs. male; RR 1.7; 95% CI 1.2–2.5; $p = 0.004$). The females subgroup was also shown to have an increased risk of moderate-severe adverse events compared to males (female vs. male; RR 1.7; 95% CI 1.4–3.5; $p < 0.001$).[8]

Studies conducted by Medeiros-Ribero et al. and Laura Boekel et al. similar to our study, group people with the autoimmune disease together.[2,8] This is mainly because of broadly similar characteristics of immune hypersensitivity. Autoimmune diseases were mainly a disorder of the adaptive immune response; thus, it could explain why no increased risk of local AEFIs was found in subjects with autoimmunity. Indeed, our study even found a decreased risk for moderate-severe pain and soreness in women with autoimmunity (RR 0.636; 95% CI 0.454–0.891; $p = 0.007$), probably due to the use of medications to control autoimmune symptoms.

On the other hand, systemic AEFIs, such as allergic reactions, may involve humoral (B cells and antibodies) and cellular (T cells) components of the adaptive immune response. Allergic responses to vaccines are generally triggered by components such as gelatin, neomycin, or adjuvants (i.e., aluminum hydroxide used in CoronaVac). This allergic reaction could be caused by hypersensitivity reaction type 1 involving IgE antibodies or, in the case of delayed-type reactions, caused by T cells mediated immune response. Other responses involving immune reactions can occur because vaccines can trigger antibodies due to the molecular similarity between the antigen on the vaccine and the host antigen.[9]

Fever, one of the AEFIs that can arise due to the innate immune response, is caused by the release of prostaglandin E2 (PGE2) and cytokines (IL-1, IL-6, and tumor necrosis factor (TNF)). Previously, it was found that fever had a significant relationship with autoimmunity, so further research is needed on the factors that can influence the differences in people with autoimmune and non-autoimmune people with fever.[10] In addition, gastrointestinal symptoms, such as nausea, vomiting, heartburn, and diarrhea, were also found to be more severe in the autoimmunity group. Again, further research is needed to determine the causes and factors that influence this observed phenomenon. Finally, the severity of headaches was also increased for the autoimmunity group following vaccination. Yet again, further research is needed to determine whether headache occurred independently or as a combination of previous systemic AEFIs described.

Our study found that after receiving the CoronaVac vaccine, autoimmune symptom relapse occurred in 19 (10.4%) out of 182 people. This result is similar to a previous New York study by Medha Barbhaiya et al. which found that of 1101 patients who received the first dose of the SARS-CoV-2 vaccine, 117 or 10% experienced a relapse. The study author concludes that relapse may occur due to mimicry of molecules that trigger immune activation or the effects of adjuvants.[11]

This study gives different data from the others described before; we exclude male respondents and limit age groups to 17–65 years old so that more consistent results regarding population groups at risk for autoimmunity could be obtained (i.e., young productive age women). We also break down the specific follow-up events to see which AEFIs have the most significant relationship or are not significantly related. The investigators also analyzed the relationship between AEFI severity and autoimmunity status and provided an overview of recurrence in the autoimmune group after receiving the CoronaVac vaccine.

Although it has several advantages, this study also has weaknesses. First, this research is conducted to compare the incidence of AEFIs, so that explanations regarding the causes and factors that influence the relationship cannot all be discussed. In addition, there are several confounding factors in the study, namely BMI and comorbidities, which were not studied.

5. Conclusion

Based on the study, it can be concluded that the AEFI is more common in PWAD than in PWOA (75.8% vs. 64.8%) after CoronaVac vaccination. It was also found that there was a significant relationship between autoimmunity with AEFI ($p = 0.01$) and systemic AEFI ($p = 0.025$). On the other hand, there was no significant relationship between autoimmunity and local AEFI ($p = 0.076$).

Disclaimer

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Declaration of competing interest

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