Adverse Event Following Immunization (AEFI) Associated With COVID-19 Vaccine Reported In A Tertiary Hospital: A Cross-Sectional Study

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Accepted: 10 December 2024

ABSTRACT

Introduction:
COVID-19 vaccine is the most effective preventive measure to curb the spread of COVID-19 infection. Monitoring of COVID-19 vaccine safety is important as no vaccine is completely risk-free and adverse events following immunization (AEFI) are possible. The aim of the study is to investigate AEFI associated with COVID-19 vaccines among adult patients visiting Hospital Kuala Lumpur (HKL). The specific objectives are to identify the types and severity of AEFI, determine the common management of AEFI and explore the associated factors that affects the severity of AEFI.

Methods:
This study was a single centre, retrospective cross-sectional study using secondary data obtained from AEFI reporting submitted to HKL. All patients who received the COVID-19 vaccine and reported AEFI were included in this study. Logistic regression analysis were used to assess associated factors that may affect the severity of AEFI.

Results:
A total of 263 AEFI reports were included in the final analysis. Majority of the patients were presented with systemic reactions (n= 207, 78.7%) and minor reactions (n = 228, 86.7%). Intravenous steroid (n=122, 46.4%) was the most common medication administered for management of AEFI. The identified factors associated with AEFI severity include the use mRNA vaccine (aOR 0.07, 95% CI 0.02-0.22, P <0.001), male gender (aOR 2.72, 95%CI 1.17-6.33, P= 0.020), presence of comorbidities (aOR 3.50, 95% CI 1.48-8.27, P= 0.004), underlying hypertension (aOR 9.88, 95% CI 1.45-67.34, P =0.019) and respiratory disease (aOR 7.73, 95% CI 1.27-47.04, P= 0.027)

Conclusion:
Majority of the reported AEFI were systemic and minor reactions. Intravenous steroid was the common drug administered for the management of AEFI. The identified factors associated with AEFI severity highlight the need for enhanced monitoring and tailored management strategies to address AEFI, particularly in individuals with known risk factors.

Keywords:
COVID-19 vaccine, AEFI, mRNA, non-mRNA

INTRODUCTION

Vaccines are critical in combating the COVID-19 pandemic because they enhance population immunity, reduce disease complications, and minimize the ongoing health catastrophe.[1] Equitable access to safe and effective vaccines are crucial and large-scale immunization program are currently ongoing worldwide.[2,3]

National COVID-19 immunization program is among the initiative implemented by Malaysian government as a strategy to manage COVID-19 pandemic.[4] Two types of COVID-19 vaccines used in Hospital Kuala Lumpur (HKL) are mRNA (Comirnaty by Pfizer) and non-mRNA vaccines such as viral vector (Vaxzevria by AstraZeneca) and inactivated virus vaccines (CoronaVac by Sinovac). Adverse events following immunization (AEFI) is defined as any unfavorable medical response that happens after immunization.[5] Monitoring on the safety of COVID-19 vaccine is important since no vaccine is entirely without risk.[5] Therefore, AEFI reporting is a fundamental component of post-approval pharmacovigilance activities to ensure the safe and appropriate use of vaccine.[3]

Although there is a rapid review comparing the safety data of various types of COVID-19 vaccine, the limitation is those data are taken from published articles and interim reports provided to them.[6] These documents may have limited information in the summarized format and individual patient data was not available, thus there is possibility of missing certain important aspects of the study.

According to World Health Organization (WHO), the severity of reactions can be divided into minor and severe reactions. Minor reaction always happens within first few hours of vaccination and recovers after a short duration of time.[5] Severe reaction is defined as reaction that can be disabling and it includes seizures and all allergic reactions to a particular component in a vaccine.[5] It also includes any serious events that is either life threatening, results in significant disability, inpatient hospitalization or death.[5] Besides, the anaphylaxis incidence rates done in a surveillance study was only 4.8 (95% CI 3.2-6.9) per million doses of mRNA vaccine which were similar to other published reports.[7]

Understanding the nature of AEFI are crucial in identifying potential issues and their implications on public health. Furthermore, disinformation on safety of COVID -19 vaccines through the mass media has caused anxiety among public.[8] Previous study reported that mild to moderate discomfort at the injection site was one of the most common recorded local reactions of the mRNA vaccinations, with less than 1.0% of patients experiencing severe pain.[9] In a pooled interim analysis of multiple studies, discomfort at the injection site (54.2%), headache (52.6%), and fatigue (53.1%) were the common AEFI.[1]

This study also intends to identify the possible factors associated with the severity of AEFI following COVID-19 vaccination. A study published in United Kingdom (UK) has found that AEFI associated with COVID-19 vaccine was found to be higher in younger female recipients.[10] The review of 87 publications also revealed that the AEFI of COVID-19 vaccine in elderly population were rather benign when compared with other population. Both the rate and severity of local and systemic reactions decreased in elderly population.[6] Individuals with hypertension and a history of allergy to any substances had a two-fold risk of getting AEFI.[11] Furthermore, another study indicated that those with hypothyroidism (OR 3.10, 95% CI 1.20-7.60) had three times the risk of experiencing AEFI.[11]

However, currently there is lack of data on AEFI of different types of COVID-19 vaccines administered to our local population. Thus, evidence on severity of AEFI is essential to maintain public confidence on safety of different types of COVID-19 vaccine. Besides, identification on the common treatment of AEFI will assist in strengthening the current management strategies and improving patient's outcome. AEFI management differs based on the nature and intensity of the AEFI reactions.[12] Therefore, this study aims to investigate the type and severity AEFI, management of AEFI and the associated factors that affect the severity of AEFI among adult patients.

METHODS

Study Design, Population, and Setting

This was a single centre, cross-sectional study conducted at HKL. Data was obtained retrospectively from AEFI reporting form submitted to Pharmacy Resource Information Centre (PRIC). The study population were adult patients (≥18 years old) who visited HKL after developing adverse event following COVID-19 vaccination from 1 February 2021 till 31 December 2021. All patients who received the COVID-19 vaccine and reported AEFI were included in this study. The exclusion criteria for this study includes patients with incomplete or irretrievable data, patients who transferred out to another hospital and patient who discharged at their own risk.

Sample Size

Raosoft sample size calculator was used to calculate the sample size. By assuming 5.0% of margin error, 95.0% of confidence level, population size of 20,000 and distribution response from literature review is 22.0%, the total calculated sample size was 261 patients.[10]

Data Collection

A data collection form was used to extract the required information from the AEFI reporting form. This form was obtained from PRIC in HKL. The data collection form consists of six sections, namely: patient's details, vaccine's details, comorbidities, type of reactions, severity of reaction and management.

The types of AEFI were classified based on several categories namely systemic or local reactions, medical dictionary for regulatory activity (medDRA) system organ class and allergic or anaphylaxis reaction.[5, 13] Severity of reactions were divided into minor and severe reactions.[5] According to World Health Organization (WHO), minor reaction refers to the reaction happens within first few hours of vaccination and recovers after a short duration of time.[5] Severe reaction is defined as reaction that can be disabling and it includes seizures and all allergic reactions to a particular component in a vaccine.[5] It also includes any serious events that is either life threatening, results in significant disability, inpatient hospitalization or death.[5]

All patient-identifiable data were removed from the data collection form and replaced with subject identification numbers to protect patient's confidentiality and privacy. All study documents and data were stored securely and only accessible to the principal investigators. Patient privacy and confidentiality were protected during any data analyses, interpretation, and publications as it devoid of any patient-identifiable data.

Statistical Analysis

The study results was reported as descriptive and inferential statistics by using IBM® Statistical Package for the Social Sciences (SPSS) version 26.

Demographic data was analysed using descriptive analysis where categorical variable was expressed as frequencies and percentages, while the continuous data was reported as median and interquartile range (IQR) for non-normally distributed data. Severity of AEFI was presented as ordinal data. All remaining data was presented as nominal data. Pearson's chi-square was used to examine the association between variable such as the severity of AEFI and types of COVID-19 vaccines.

Simple logistic regression was performed. Variables with a *P*-value <0.25 were included in multiple logistic regression analysis where backward stepwise/forward likelihood method was applied to assess independent factors associated with severity of AEFI. Multiple logistic regression analysis was done to assess the factors associated with severe AEFI. Result was presented as odds ratio (OR) and 95% confidence interval (CI). All statistical tests with a *P*-value of <0.05 denotes statistical significance.

RESULTS

Type of AEFI

A total of 505 AEFI cases due to COVID-19 vaccine were reported from February 2021 to December 2021 in HKL. However, only 263 cases fulfilled all the inclusion criteria in this study. Majority of patients were presented with systemic reaction (n= 207, 78.7%) such as fever and others were presented with local reactions like pain and redness on injection site (Table 2). The most common systemic reaction observed in this study was fever. Besides, high proportions of AEFI involving skin and subcutaneous disorder reported received mRNA vaccine (n=126, 64.6%). Nevertheless, majority of the AEFI reported were not anaphylaxis reaction (n=255, 97.0%).

Severity and Management of AEFI

Majority of the reported AEFI were minor reactions (n=228, 86.7%) following COVID-19 vaccination. Pearson's chi-square test showed that a higher number of patients experiencingsevere AEFI received non-mRNA (n= 30, 85.7%) compared to mRNA COVID-19 vaccine (n=5, 14.3%) (P<0.001). A total of 31 reports involved serious reactions with only minority of the reported AEFI were life-threatening reactions (n=10, 3.8%). The majority of the reported cases were not serious reactions (n=232, 88.2%).

In terms of management of AEFI, the common medications administered are intravenous (IV) steroids (n=122, 46.4%) followed by oral paracetamol (n=75, 28.5%). Only minority of patients were not given any medications (n=24, 9.1%) (Table 4).

Factors Associated with Severity of AEFI

Simple logistic regression analysis revealed that the significant factors associated with severity of AEFI were male gender, mRNA type of vaccine, first dose of COVID- 19 vaccine, chinese, age 55 years old and above and presence of comorbidities. All variables with a P-value less than 0.25 were included in the multiple logistic regression analysis to assess the independent factors associated with severity of AEFI (Table 5).

Backward LR multiple logistic regression method was applied and the result showed that the significant factors associated with the severity of AEFI were male gender, mRNA type of COVID-19 vaccine, presence of comorbidities, patient with underlying respiratory disease or hypertension. The multiple logistic regression model was able to classify 87.8% of cases correctly. Hosmer and Lemeshow test was used to examine the final model, the result confirmed that the model was a good fit for the data (χ^2 = 2.12, P = 0.832). Logistic regression showed that no interaction nor multicollinearity detected. Area under ROC curve is 0.860 (95% CI 0.81- 0.92, P< 0.001). The model can accurately discriminate 86.0% of cases.

Table 1. Demographics and clinical characteristics (n=263)

Parameters	n (%)
Age	
Median ± IQR, in years	34 ±15
18-30 years	95 (36.1)
31-40 years	89 (33.8)
41-50 years	41 (15.6)
51-60 years	18 (6.8)
61-70 years	13 (4.9)
71-80 years	5 (1.9)
81-90 years	2 (0.8)
Gender	
Male	74 (28.1)
Female	189 (71.9)
Race / Nationality	
Malay	179 (68.1)
Chinese	47 (17.9)
Indian	26 (9.9)
Others*	11 (4.2)
Allergy status	
Drug allergy	25 (9.5)
Food allergy	20 (7.6)
Both drug and food allergy	8 (3.0)
No known drug or food allergy	210 (79.8)
Healthcare worker	
Yes	61 (23.2)
No	202 (76.8)
Type of vaccine	
mRNA	157 (59.7)
non-MRNA	106 (40.3)
Number of doses	
First dose	138 (52.5)
Second dose	125 (47.5)
Comorbidities	
Yes	79 (30.0)
No	184 (70.0)
Type of comorbidities	
Coronary artery disease	5 (1.9)
Diabetes mellitus	18 (6.8)
Dyslipidemia	8 (3.0)
Gastrointestinal disease	1 (0.3)
Hypertension	20 (7.6)
Thyroid disease	1 (0.3)
Renal disease	2 (0.8)
Respiratory disease	17 (6.4)
Rheumatoid arthritis	1 (0.3)
Skin disease	2 (0.8)
Allergic rhinitis	1 (0.3)
Other disease	3 (1.1)
History of COVID-19 infection	
Yes	0 (0.0)
No	263 (100.0)

*Include permanent residents and foreigner

Table 2. Type of AEFI for different type of COVID-19 vaccine

AEFI	Total (N)	Type of vaccine, n (%)	
		mRNA (n=157)	Non-mRNA (n=106)
Type of reaction*			
Systemic	207	132 (63.8)	75 (36.2)
Local	136	72 (52.9)	64 (47.1)
Systemic reaction (n=207)			
Fever	70	53 (75.7)	17 (24.3)
Chills and rigors	13	11 (84.6)	2 (15.4)
Myalgia	6	4 (66.7)	2 (33.3)
Arthralgia	2	1 (50.0)	1 (50.0)
Headache/ dizziness	61	44 (72.1)	17 (27.9)
Nausea/ vomiting	13	8 (61.5)	5 (38.5)
Diarrhea	2	1 (50.0)	1 (50.0)
Palpitation	9	5 (55.6)	4 (44.4)
Other reactions	31	5 (16.1)	26 (83.9)
Local reaction (n=136)			
Pain at site of injection	17	9 (52.9)	8 (47.1)
Numbness	17	13 (76.5)	4 (23.5)
Swelling	15	4 (26.7)	11 (73.3)
Redness	2	1 (50.0)	1 (50.0)
Swollen armpit	1	1 (100.0)	0 (0.0)
Rashes	52	34 (65.4)	18 (34.6)
Itchiness	22	10 (45.5)	12 (54.5)
Other reactions	10	1 (10.0)	9 (90.0)
medDRA system organ class*			
Cardiac disorder	23	9 (39.1)	14 (60.9)
Musculoskeletal & connective tissue disorder	31	20 (64.5)	11 (35.5)
Nervous system disorder	56	37 (66.1)	19 (33.9)
Respiratory, thoracic and mediastinal disorder	25	5 (20.0)	20 (80.0)
Vascular disorder	4	1 (25.0)	3 (75.0)
Gastrointestinal disorder	32	22 (68.8)	10 (31.3)
Eye disorder	1	0 (0.0)	1 (100.0)
General disorder and administration site condition	74	39 (52.7)	35 (47.3)
Skin & subcutaneous disorder	195	126 (64.6)	69 (35.4)
Allergy reaction			
Yes	47	6 (12.8)	41 (87.2)
No	216	151 (69.9)	65 (30.1)
Types of allergy reaction*			
Skin urticarial or pruritus	33	5 (15.15)	28 (84.8)
Angioedema	4	1 (25.0)	3 (75.0)
Conjunctival erythema	1	0 (0.0)	1 (100.0)
Others	9	0 (0.0)	9 (100.0)
Anaphylaxis			
Yes	8	2 (25.0)	6 (75.0)
No	255	155 (60.8)	100 (39.2)

*Total reactions for type of reaction, medDRA system organ class and type of allergy reaction are more than 100% as some patients presented with multiple reactions.

Table 3. Severity and outcome of AEFI for different type of COVID-19 vaccine (n=263)

Outcomes	Total (N)	Type of vaccine, n (%)	
		mRNA (n=157)	Non-mRNA (n =106)
Classification of reaction			
Minor	228	152 (66.7)	76 (33.3)
Severe	35	5 (14.3)	30 (85.7)
Seriousness of the reaction			
Life-threatening	10	0 (0.0)	10 (100.0)
Caused or prolonged hospitalization	19	2 (10.5)	17 (89.5)
Caused disability or incapacity	2	0 (0.0)	2 (100.0
Caused birth defect	0	0 (0.0)	0 (0.0)
Not serious	232	155 (66.8)	77 (33.2)
Outcome			
Recovered fully	84	76 (90.4)	8 (9.6)
Recovering	166	79 (47.6)	87 (52.4)
Not recovered	10	2 (20.0)	8 (80.0)
Unknown	3	1 (33.3)	2 (66.7)
Vaccine reaction relationship			
Certain	38	32 (84.2)	6 (15.8)
Probable	169	96 (56.8)	73 (43.2)
Possible	50	29 (58.0)	21 (42.0)
Unlikely	6	1 (16.6)	5 (83.4)
Admitted to ward			
Yes	29	6 (20.7)	23 (79.3)
No	234	152 (64.9)	82 (35.1)
In-hospital mortality			
Yes	8	1 (12.5)	7 (87.5)
No	255	157 (61.6)	98 (38.4)

Table 4. Medications used in management of AEFI

Management	AEFI, n (%)		
	Total (N)	Minor (n=228)	Severe (n=35)
No drugs	24 (9.1)	20 (8.8)	4 (11.3)
IV steroid	122 (46.4)	101 (44.3)	21 (60.0)
IV antihistamine	3 (1.1)	3 (1.3)	0 (0.0)
Intramuscular adrenaline	1 (0.4)	0 (0.0)	1(2.9)
Oral steroid	5 (1.9)	4 (1.8)	1 (2.9)
Oral antihistamine	6 (2.3)	6 (2.6)	0 (0.0)
Oral paracetamol	75 (28.5)	74 (32.5)	1 (2.9)
Oral NSAIDS	2 (0.8)	2 (0.9)	0 (0.0)
IV metoclopramide	8 (3.0)	7 (3.0)	1 (2.9)
Others	17 (6.5)	11 (4.8)	6 (17.1)

Table 5. Simple and multiple logistic regression analyses of factors associated with severity of AEFI following COVID-19

Associated factors	Minor AEFI	Severe AEFI	Simple logistic regression		Multiple logistic regression	
			Crude odds ratio (95% CI)	*P*-value	Adjusted odd ratio (95% CI)	*P*-value
Gender						
Male	56	18	3.25 (1.57-6.74)	0.002	2.72 (1.17-6.33)	0.020
Female	172	17	Reference		Reference	
Type of vaccine						
mRNA	152	5	0.08 (0.03-0.22)	<0.001	0.07 (0.02-0.22)	<0.001
Non-mRNA	76	30	Reference		Reference	
No of doses						
1	111	27	3.56 (1.55-8.16)	0.003		
2	117	8	Reference			
Ethinicity						
Malay	160	19	Reference	0.150		
Chinese	36	11	2.57 (1.13-5.88)	0.025		
Indian	23	3	1.10 (1.10-0.30)	0.887		
Others	9	2	1.87 (0.38-9.30)	0.444		
Age by category (years)						
<55	212	21	Reference	<0.001		
≥55	16	14	8.83(3.72-20.58)			
History of drug allergy						
Yes	22	3	0.88 (0.25-3.10)	0.84		
No	206	32	Reference			
Presence of comorbidities						
Yes	45	17	3.84 (1.83-8.04)	<0.001	3.50 (1.48-8.27)	0.004
No	183	18	Reference		Reference	
Type of comorbidities**						
Coronary artery disease	4	1	1.65 (0.18-15.78)	0.660		
Diabetes mellitus	12	6	2.76 (0.92-8.28)	0.071		
Dyslipidemia	4	1	1.65 (0.18- 15.18)	0.660		
Hypertension	6	3	2.96 (0.73-12.03)	0.129	9.88 (1.45-67.34)	0.019
Respiratory disease	9	3	2.28 (0.59-8.87)	0.234	7.73 (1.27-47.04)	0.027

Backward LR multiple logistic regression method applied in all analyses.
No interaction and multicollinearity detected.
Hosmer–Lemeshow Test $\chi 2 = 2.12$, df = 5, $P = 0.832$; Overall classification table = 87.8%; Area under ROC curve = 86.0%
**P* value <0.05 denotes statistical significance
***The reference group for type of comorbidities is patients without these conditions

DISCUSSION

This study assessed on the characteristic and severity of AEFI reported in tertiary referral hospital in Malaysia. Majority of patients reported with systemic reaction cases received mRNA vaccine (n= 132, 63.8%). This finding contrast with a study conducted in the UK where systemic reaction were less frequent among patient who received mRNA vaccine (n= 38155, 6.1%).[10] In this study, half of the patients reported with local reactions received mRNA vaccine (n=72, 52.9%). This finding was similar to a systematic review and meta-analysis which demonstrated that majority of local reaction cases reported were recipients of mRNA vaccine. (n=31735, 79.9%).[15]

In terms of hypersensitivity reactions, only 17.9% from the reported AEFI were allergy reactions. The incidence rate of allergy reaction demonstrated in a phase 3 trial in a Turkey study was below 0.1%.[16] There were several mechanism causing anaphylaxis reactions such as via cross liking with IgE or other pathway such as antibody dependent activation of complement or IgG mediated mast cell activity.[17] This study was not able to quantify the exact incidence rate of allergic reaction as the information on total number of vaccine recipient were not available.

In terms of severity of reactions, majority of the AEFI reported were minor reactions (n=228, 86.7%). Only 14.3% of reported severe reactions were mRNA vaccine recipients. Besides, a systematic review revealed that less than 1 % of patient reported with severe reactions received viral vector vaccines.[26] Another study conducted in India also demonstrated that there were no severe reactions reported from inactivated virus vaccine.[18] These findings depicts the good safety profile in different type of the COVID-19 vaccine globally.

Even though mRNA was the most common type of COVID-19 vaccines administered to our local population, however rare AEFI such as myocarditis and pericarditis were not reported in this study and multiple studies conducted in different country like Nepal, India and Korea.[7] [10,18] Several cases of myocarditis or pericarditis were reported in a surveillance study of mRNA vaccines however the study concluded that there was no significant association between myocarditis or pericarditis with mRNA vaccine.[9]

In terms of management of AEFI, the common medications administered were steroid (48.3%) and paracetamol (28.5%). Similar findings were observed in several studies done in India, Nepal and Korea where the most common medications prescribed was paracetamol.[7,10,18] The common AEFI experienced by majority of vaccine recipient in multiple studies were fever and headache.[18,19] Steroid may have emerge as the common medications administered in this study due to higher proportion of patient experienced allergy (n=47, 17.9%) and anaphylaxis reaction (n=8, 3.0%) compared to other studies conducted abroad (0.1%-1.7%). [7,10,11] Knowledge on common management of AEFI was crucial in providing valuable data that may lead to improvement in vaccination practice and assist in enhancing the overall effectiveness and safety of immunization programs.

There were several significant independent factors that were associated with elevated risk of severe AEFI. Based on multiple logistic regression analysis, male gender (*P* =0.020), patient with comorbidities (*P* =0.004) such as underlying hypertension (*P* =0.019) or respiratory disease (*P* =0.027) were associated with higher odds of developing severe AEFI. On the other hand, mRNA type of vaccine (*P* <0.001) were found to be significantly associated with lower odds of the developing of severe AEFI.

Majority of AEFI reported in this study was female patients (n= 189, 71.9%) however logistic regression demonstrated that male patients was associated with higher odds of developing severe AEFI. This finding was contradictory with several studies conducted abroad. According to a report obtained from four cross sectional studies conducted on mRNA vaccine, severe AEFI were more frequent among females compared to male.[20] A study on mRNA and viral vector vaccines found that female (16.2%) were more likely to report AEFI (OR 1·89; 95% CI 1·85–1·94, *P*<0·001) compared to male (9.3%).[10] Another study conducted in Korea found that 76.7% of patients reported AEFI following viral vector vaccine are females.[7] The biological mechanism for females having a higher frequency of AEFI could be because both Angiotensin- Converting Enzyme 2 and Angiotensin II receptor type 2 gene were located on the X chromosome and thus enhancing the immune response.[20]

Besides, patient with comorbidities were found to have higher odds of developing severe AEFI. This finding is inconsistent with an observational study conducted in India where there were no association found between presence of comorbidities and severity of AEFI.[21] However, a multi-national study done in Arab showed that the presence of comorbidities is one of the significant factors associated with AEFI.[22] Another cohort study also revealed that the occurrence of AEFI is significantly associated with the presence of comorbidities.[23] This could be due to presence of comorbidities may affect the immune system response to vaccines, thereby elevating the risk of severe AEFI.

In terms of type of comorbidities, this study found that patient with underlying hypertension or respiratory disease were at higher risk of developing severe AEFI. This finding was proportional with a study conducted in India where individual with hypertensive were at higher risk of developing AEFI.[11] Patient with underlying respiratory disease like asthma was having higher odds of developing severe AEFI could be due to underlying inflammation of the disease which enhance the immune response to vaccination.

The findings from this study provides an overview on the AEFI associated with COVID-19 vaccine in HKL. This study also provides important data on the clinical profiles of patient who experienced AEFI associated with COVID-19 vaccines. The essential information obtained from the factors that may affect the severity of AEFI outcome may serve as a guide for clinicians to evaluate patient's prognosis accurately and manage patient appropriately based on patient's demographic data and clinical characteristic. Clinicians can also better stratify patient's risk based on the symptoms of AEFI that patient develop after COVID-19 vaccination. It was important to take note that the significant factors that may influence the severity of AEFI were mRNA type of vaccine and patient with underlying comorbidities.

Besides, variation in severity reaction incidences found in multiple studies may be due to the utilization of different severity classification tool such as MedRA or United States Food and Drug Administration (USFDA) classification.[2,11] Some studies classify the severity based on questionnaire where patient self-rated their severity of reaction.[24,25] Therefore, utilization of different severity assessment tool could affect the study outcome.

As current study found that mRNA vaccine was one of the independent factors that was associated with lower odds of developing severe AEFI, it would be interesting to explore further on the different brand of mRNA vaccines that may affect the severity of AEFI. Proper identification of factors would be important to minimise the risk of severe AEFI. Besides, immunogenicity test should be conducted in future studies in order to establish the causality between the AEFI and COVID-19 vaccines.

There were several limitations in this study. This study's inherited retrospective observational nature would affect the data quality primarily due to recall bias in the documentation and incomplete information in AEFI form. Lastly, this study was a single centre cross-sectional study carried out in a tertiary care centre in capital of the country, therefore the prevalence of the result obtained in this study may not represent all the healthcare facilities available in Malaysia.

On the other hand, the baseline demographic data, clinical characteristic, type and severity of AEFI may be different across other states in the country. Therefore, a multicentre randomised controlled study should be conducted in the future to allow better generalisation of results and more accurate findings. Larger and longer duration of randomized clinical trials would be able to provide a more appropriate idea on the overall efficacy and safety of COVID-19 vaccines. Further evaluation on safety profile of different type of COVID-19 vaccine booster dose is recommended.

CONCLUSION

In conclusion, majority of the reported AEFI were systemic and minor reactions. Steroid was the most common drug administered for the management of AEFI. The identified associated factors of AEFI severity highlight the need for enhanced monitoring and tailored management strategies to address AEFI, particularly in individuals with known risk factors.

ACKNOWLEDGEMENT

I would like to take this opportunity to thank everyone who has helped me in completing this project. Firstly, I would like to express my gratitude to my family members for being my constant spiritual support for me to move forward through the challenging times with my thesis. Besides, I would also like to thank all my lecturers for their kind words and suggestions that lead me through the obstacles along the journey of my research. This research would not have been possible without their invaluable education, continuous motivation, encouragement, and blessings.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICAL APPROVAL

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-21-02413-YAV) and the Hospital Canselor Tuanku Muhriz Ethics Committee (UKM PPI/111/8/JEP-2022-232) with compliance to the Guidelines on Good Clinical Practice (GCP) and Declaration of Helsinki.

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