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Original article

Factors associated with the inflammatory immune response induced by COVID-19 vaccines among adults

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Abstract: In efforts to counteract the COVID-19 pandemic, several vaccines have been developed. Despite their efficacy, they are not without adverse immune reactions that may occur among populations according to various factors. The purpose of this study was to explore some factors that are associated with the inflammatory immune response induced by COVID-19 vaccines among the Libyans. This analytical study was performed on recorded data for 410 individuals who received three different COVID-19 vaccines (Sinovac, AstraZeneca-Oxford and Sputnik-V) that were retrieved from the previous study on December 2nd, 2023. Among 410 Libyan adults, 404 cases were enrolled for the final analysis, 56.7% (CI 95%, 52.0 - 61.1) of the vaccinated experienced systemic inflammatory reactions. Wherein, Sinovac vaccine recipients were more likely to experience inflammatory reactions compared to AstraZeneca-Oxford vaccine recipients with a high significant (χ^2_{MH} = 38.344, P = 0.001) adjusted odds ratio equal to 5.234 (CI 95%, 3.034 - 9.029). After controlling for confounding factors, age, gender and comorbidity were found to significantly associated risk factors with an inflammatory response among AstraZeneca-Oxford vaccine recipients (P = 0.001, P = 0.021 and P = 0.002, respectively). Whereas comorbidity was only one of the significantly increased risk factors associated with the occurrence of inflammatory events among Sinovac vaccine recipients (χ^2 = 7.507, P = 0.006). In conclusion, age, gender, comorbidity and type of vaccine were found to be significant risk factors for the occurrence of inflammatory events induced by vaccines. Further studies with larger sample size and the inclusion of laboratory parameters such as C-reactive protein and alpha-1-acid glycoprotein along with antibodies are needed.

Introduction

Several vaccines have been developed with different biological and pharmaceutical ingredients utilizing various technologies in order to counteract the COVID-19 pandemic [1]. Adenovirus vectors are one of the delivery techniques that are used in authorized COVID-19 vaccines. Different types are used such as chimpanzee adenovirus Y25 that is used in the AstraZeneca-Oxford COVID-19

vaccine and two recombinant human adenoviruses (ad26 and ad5) that are used in the production of the Sputnik-V vaccine [2 - 5]. In addition, the fact that pre-existing immunity against the adenovirus vectors is a special feature of this type of vaccine as well as the ability to induce immune responses against the vector particles which can impair the response to the vaccine antigen and that may play a role in the immune response against booster doses of the COVID-19 vaccines [1, 6 - 10].

Chinese CoronaVac (Sinovac) is an authorized COVID-19 vaccine made up of virus particles that are being grown in Vero cells and inactivated by beta-propiolactone (BPL) to lose their ability to cause disease while still inducing an inflammatory response against S proteins [11 - 13]. The Sinovac vaccine is produced through several steps of virus purification, yielding a final product that primarily contains viral proteins and is composed of nearly pure viral particles [14 - 15]. Consequently, the quality and variations in the efficacy observed in the studies which are believed to be caused by altering the ratios of pre-fusion and post-fusion conformations of S proteins as a result of variation in production steps [1, 16]. Unlike genetic vaccines that are referred to as being self-adjuvant because they have the potential to induce innate responses, protein-based vaccines such as inactivated whole-virus vaccines are typically unable to induce a sufficient immune response on their own and require adjuvant, as a result, an aluminum hydroxide substance is used with the Sinovac vaccine to enhance the immune response [11, 17 - 20].

Even though the effectiveness of the vaccines in limiting COVID-19's spread as well as reducing the risk of complications and even death [21 - 24]. Like other vaccines, they are not without adverse reactions that may vary in prevalence among population according to various factors [25 - 27]. Which are not limited to factors that are related to the vaccine itself (i.e., brand, dose, type and adjuvant used) but there are several other factors such as intrinsic characteristics (i.e., age, gender, ethnicity and comorbidity) and delivery factors (i.e., injection route) that may influence the generation of the immune response and, therefore, the safety and effectiveness of the vaccines [1, 23 - 25]. Consequently, there is a need to investigate factors associated with the inflammatory immune response stimulated by COVID-19 among individuals in Libyan population [28]. As a result, this study aimed to explore certain factors that are associated with the inflammatory immune response induced by COVID-19 vaccines in Libya.

Materials and methods

Study design and data retrieval: This analytical study was performed on recorded data for 410 individuals who received the first dose of one of the three COVID-19 vaccines (Sinovac, AstraZeneca-Oxford or Sputnik-V). The data included demographic variables (age and gender), clinical profile (comorbidity and history of COVID-19 incidence), vaccine received and reactogenicity which were retrieved from the previous published study [28].

Data analysis: The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistic was carried out using percentage and frequency representing in tables after discretizing the continuous variable with the entropy-MDL algorithm using Orange software version 3.33.0. Fisher's exact and Chi-square tests at a significant level of $P < 0.05$ were used to find the associated risk for developing inflammatory immune reactions. 95% confidence intervals of the risk ratio and adjusted odds ratio for measuring effect size as well as the Mantel-Haenszel and Breslow-Day tests for measuring association with controlling confounding factors were calculated [29].

Results

Baseline characteristics of the data: Among the 410 individuals, six cases that had only local events were excluded while the remaining cases were enrolled for final analysis (n = 404). **Table 1** demonstrates the baseline characteristics of the individuals based on the vaccine received, wherein, the percentage of AstraZeneca-Oxford vaccine recipients was 56.2% followed by the percentage of Sinovac and Sputnik-V vaccine recipients which

were 34.9% and 08.9%, respectively. In general, 83.4% (CI 95%, 80.0 - 86.6) of the cases were within the range of 18 to 61 years of age. In addition, 53.5% (CI 95%, 48.6 - 57.9) of overall cases were females. Furthermore, 23.0% (CI 95%, 19.3 - 27.0) of the cases had at least one chronic disease and a total of 56.7% (CI 95%, 52.0 - 61.1) of those vaccinated were reported with at least one systemic inflammatory response, since only 04.7% (CI 95%, 3.0 - 6.4) of the cases had the COVID-19 disease.

Table 1: Baseline characteristics of COVID-19 vaccines recipients

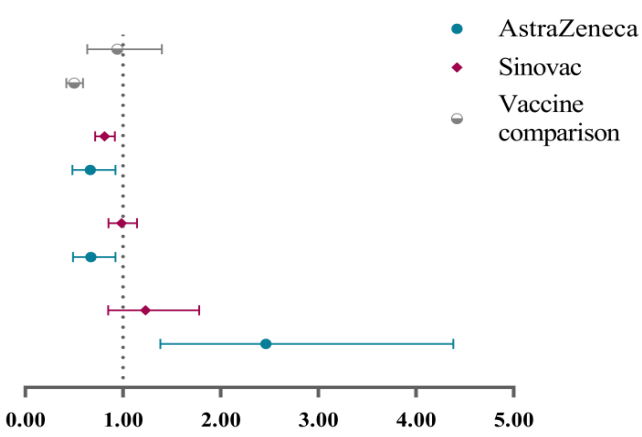
		Vaccines			Total	CI 95%	
		AstraZeneca	Sputnik-V	Sinovac		Lower	Upper
Adverse Effects	No	132 (58.1%)	20 (55.6%)	023 (16.3%)	175 (43.3%)	38.9	48.0
	Yes	095 (41.9%)	16 (44.4%)	118 (83.7%)	229 (56.7%)	52.0	61.1
Gender	Male	113 (49.8%)	16 (44.4%)	059 (41.8%)	188 (46.5%)	42.1	51.2
	Female	114 (50.2%)	20 (55.6%)	082 (58.2%)	216 (53.5%)	48.6	57.9
Age in Years	18 - 61	176 (77.5%)	33 (91.7%)	128 (90.8%)	337 (83.4%)	80.0	86.6
	> 61	051 (22.5%)	03 (08.3%)	013 (09.2%)	067 (16.6%)	13.4	20.0
In. with COVID19	No	221 (97.4%)	35 (97.2%)	129 (91.5%)	385 (95.3%)	93.3	97.0
	Yes	006 (02.6%)	01 (02.8%)	012 (08.5%)	019 (04.7%)	03.0	06.4
Comorbidity	No	189 (83.3%)	28 (77.8%)	094 (66.7%)	311 (77.0%)	73.0	80.9
	Yes	038 (16.7%)	08 (22.2%)	047 (33.3%)	093 (23.0%)	19.3	27.0
Total		227 (56.2%)	36 (08.9%)	141 (34.9%)	404 (100%)		

Confidence interval level of 95% was calculated with Bias-corrected and accelerated (BCa) method based on 10000 bootstrap samples.

Inflammatory reactions and demographic characteristics: The risk of an inflammatory reaction among the individual group of 18 to 61 years of age who received the AstraZeneca-Oxford vaccine was 2.951 (CI 95%, 1.557 - 5.590) as high as the risk of inflammatory events among their older counterparts (**Figure 1**). The value of the Mantel-Haenszel test demonstrated that after adjusting for gender and comorbidity, age was associated with the inflammatory reactions generated against the vaccine (χ^2_{MH} = 14.555, P = 0.001). Wherein, the adjusted odds ratio (AOR) indicates that these individuals (18 to 61 years of age) had 4.799 times (CI 95%, 2.106 - 10.933) the odds of experiencing inflammatory events than their older counterparts (> 61 years old) with homogeneous odds ratios across each stratum (χ^2_{BD} = 1.089, df = 03, P = 0.780). Regarding gender, 40.0% of AstraZeneca-Oxford vaccine recipients who experienced inflammatory reactions were males, who had 0.673 times (CI 95%, 0.490 - 0.924) the risk of an inflammatory response (a 32.7% decrease in risk) compared to the female subjects (**Figure 1**). The adjustment for age and comorbidity revealed that gender was significantly associated with the inflammatory response stimulated by the vaccine (χ^2_{MH} = 5.292, P = 0.021). Hence, female subjects had a higher AOR to experience inflammatory events following AstraZeneca-Oxford 2.031 times (CI 95%, 1.151 - 3.583) than their male counterparts with a homogeneous odds ratio across each stratum (χ^2_{BD} = 1.362, df = 03, P = 0.715). On the other hand, age and gender were not significantly associated with the inflammatory response among the Sputnik-V and Sinovac vaccine recipients (**Figure 1**).

Figure 1: Comparison of the risk of experiencing inflammatory reactions induced by COVID-19 vaccines

Factors	N	P-value	Estimate	95% CI
Type of vaccine				
AstraZeneca/Sputnik-V	227/036	0.770	0.942	[0.634;1.399]
AstraZeneca/Sinovac	227/141	0.000	0.500	[0.422;0.593]
Comorbidity				
Health/Illness	094/047	0.006	0.811	[0.716;0.918]
Health/Illness	189/038	0.028	0.667	[0.482;0.924]
Gender				
Male/Female	059/082	0.862	0.987	[0.851;1.145]
Male/Female	113/114	0.012	0.673	[0.490;0.924]
Age				
Younger/Older	128/013	0.227	2.463	[1.384;4.383]
Younger/Older	176/051	0.000	1.230	[0.850;1.780]



Data show the risk ratio with an upper and lower bound for the COVID-19 vaccines recipients experiencing an inflammatory reaction and their relationships with the major factors, whereas Fisher's exact and Chi-square tests were used to calculate the P-value with a significant level of 0.05.

Inflammatory reactions and medical anamneses: Although the comorbidity was significantly associated with the inflammatory response induced by each of the AstraZeneca-Oxford (χ^2 = 4.828, P = 0.028) and Sinovac vaccines (χ^2 = 7.507, P = 0.006). Wherein, for each of the AstraZeneca-Oxford and Sinovac vaccines, the risk of experiencing inflammatory events among individuals in a good health was 0.667 (CI 95%, 0.482 - 0.924) and 0.811 (CI 95%, 0.716 - 0.918) times as high as the risk of experiencing inflammatory events compared to individuals with one or more chronic illnesses (a 33.3% and 18.9% decrease in risk, respectively) (**Figure 1**). Additionally, age and gender adjustment revealed that AstraZeneca-Oxford recipients with chronic illnesses had an AOR 3.730 (CI 95%, 1.638 - 8.496) times higher than their counterparts without chronic illnesses with a significant association between comorbidity and inflammatory reactions induced by the vaccine (χ^2_{MH} = 9.360, P = 0.002) in which the odds ratios were homogeneous (χ^2_{BD} = 0.185, df = 03, P = 0.980). Whereas, there was not a significant association between stimulated inflammatory reactions and a certain chronic illness that involved: diabetes mellitus (14.6%), cardiovascular disease (07.4%), respiratory disorders (01.7%) and others (02.5%), or certain medications: anti-hyperglycemic drugs (14.4%), cardiovascular drugs (07.2%), anti-inflammatory drugs (03.5%) and others (02.0%) for each vaccine. Moreover, that inflammatory response was not statistically associated with the previous incidence of COVID-19 disease for each vaccine.

Inflammatory reactions and type of vaccine: The results demonstrated considering the recipients of the AstraZeneca-Oxford vaccine as a reference group, the risk ratio for the reference group was 0.500 (CI 95%, 0.422 - 0.593) times as high as the risk of experiencing inflammatory events than the recipients of the Sinovac vaccine which was statistically significant (χ^2 = 62.448, P = 0.000) (**Figure 1**). The common odds ratio indicated that after adjusting for age, gender and comorbidity, the recipients of the Sinovac vaccine had 5.234 (CI 95%, 3.034 - 9.029) times the odds of experiencing inflammatory reactions compared to the reference group, which was statistically significant (χ^2_{MH} = 38.344, P = 0.000) with a homogeneous odds ratio across each stratum (χ^2_{BD} = 3.479, df = 07, P = 0.837). Whereas, the risk ratio of experiencing inflammatory events in the reference group compared to Sputnik-V vaccine recipients was not statistically significant.

Discussion

The present study revealed that among Libyan adult subjects, about half of those vaccinated experienced at least one systemic inflammatory reaction, since 83.4% of the total individuals were under the age of 60 years and 77.0% of the recipients of the vaccines had one or more chronic diseases, in which age, gender and comorbidity were found to be significant risk factors for the occurrence of inflammatory events in AstraZeneca-Oxford vaccine recipients, wherein, in these individuals, females and those with at least one chronic illness were more likely to experience inflammatory events after receiving the AstraZeneca-Oxford vaccine. The present findings are in line with Almufty et al.'s findings [26] which suggested that young age, females and comorbidity are significant risk factors for experiencing adverse reactions. Menni and others [30] have also confirmed that age, gender and comorbidity are associated with experiencing adverse events. Although the study of Alemayehu et al. [31] which was performed in Eastern Ethiopia on Astra Zeneca-Oxford vaccine recipients indicated adverse events are significantly higher in the age group of 50 - 60 years old with one or more chronic illnesses than their counterparts. However, the present study contradicted the findings that indicated males are more likely to develop symptoms than female subjects. As well as, Al Bahrani et al. [32] have conducted at the King Fahad Military Medical Complex, Dhahran, during the vaccination campaign in the KSA suggested older individuals and male subjects are more likely to report adverse reactions compared to their female counterparts. These contract findings could have resulted from ethnic differences in the study populations and the Adenovirus-vector used in the vaccine which could also have triggered different immunological reactions that require further investigations [1, 25].

Regarding Sinovac vaccines, comorbidity was the only significant risk factor associated with experiencing an inflammatory event. This finding contrasts studies done by Riad et al. [27] in Turkey among health care workers, Abbas et al. [33] in Pakistan at the Foundation University College of Dentistry, Islamabad and Nurzak et al. [34] that was conducted in December 2021 at the public health center of Marosn, South Sulawesi, Indonesia, which suggested age, gender and the previous incidence of COVID-19 were significantly associated with an increased risk of inflammatory events. This observation was unclear and requires further studies, as this study had limitations represented by the relatively small sample size and the fact that the study was predominated by individuals without a history of incidence of COVID-19 disease. Therefore, more studies with a large sample size and a better infected-to-uninfected COVID-19 disease ratio to investigate the factors associated with the inflammatory reactions including laboratory parameters such as C-reactive protein and alpha-1-acid glycoprotein along with antibodies are needed.

Conclusion: Sinovac vaccine recipients were more likely to experience inflammatory reactions compared to the other vaccines. Age, gender, comorbidity and type of vaccine were the risk factors associated with the occurrence of inflammatory events induced by vaccines that should be considered.

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Author declarations: Both authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

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