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Original Article

Side effects following COVID-19 vaccination: A cross-sectional survey with age-related outcomes in Saudi Arabia

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ABSTRACT

Side effects represent a major determinant of vaccination acceptance. With the newly developed COVID-19 vaccines, there is a growing need for more investigations on vaccination safety, in real practice. With this growing need, the current study investigated the side effects experienced during days 1, 2, and 3 after the first dose of the Oxford–AstraZeneca vaccine among vaccine recipients at King Abdullah bin Abdulaziz University Hospital (KAAUH), Riyadh, Saudi Arabia. A particular emphasis was how age (≤50-year-old versus >50-year-old) affects the frequency and the severity of the side effects. A cross-sectional study was performed using a telephone-based survey. The study involved individuals who received the first dose of the Oxford–AstraZeneca COVID-19 vaccine from February 28 – March 12, 2021, at KAAUH. A total of 528 vaccine recipients were involved, of whom 77.5% were ≤50 years old. The common side effects were myalgia, headache, and fever. Adults aged ≤50 years old showed a higher incidence and intensity of reactions than the >50-year-old group. Areas, where significant differences have been, found included myalgia, headache, fever palpitation, sore throat, and gastrointestinal symptoms (p-value is less than 0.05 for all). The COVID-19 vaccine was safe and well-tolerated. The ≤50-year-old group was more prone to side effects compared to the >50-year-old group. Further studies are needed to more establish such an observation.

Keywords: Coronavirus disease, Vaccination, Oxford–AstraZeneca vaccine, Adverse effects, Safety

Introduction

The novel Coronavirus disease (COVID-19 disease) was documented at the end of December 2019 in Wuhan, China [1-3]. Since its outbreak, the Coronavirus disease has caused considerable harm and challenges to all countries around the globe. By 10 August 2021, there were around 205 million Coronavirus cases and an estimated rate of death of 4.3 million people around the world [4]. Safe and highly efficacious vaccines are needed to control the pandemic. As of March 2021, around seven vaccines are available in different countries. Currently, 60 vaccines are in clinical development stages [5]. Among the widely used vaccines are that produced by Pfizer-BioNTech, Moderna, Johnson and Johnson [6], Oxford–AstraZeneca [7], and Sinopharm [8].

Even though vaccination has its highest potential to control the coronavirus pandemic, some side effects might appear after taking the vaccine. Most of the side effects last for few days. Potential systemic side effects, for the different types of vaccines, include tiredness, headache, muscle pain, chills, and fever. Local side effects at the injection site comprise pain, redness, and swelling [6].

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Riad *et al*. conducted a survey study to investigate the side effects following Pfizer–BioNTech COVID-19 vaccine use. The most frequent side effects were pain at the injection site, fatigue, headache, muscle pain, and chills. The side effects disappeared after three days for 33% of the study participants. The prevalence of the side effects was more in the ≤43-year-old group [9]. Comparable common side effects were reported during clinical trials in China [10, 11]. Side effects after the Sinopharm vaccine, from clinical trials and real-world practice, were comparable to that of other vaccines [12, 13]. Common side effects reported from Saudi Arabia, due to Pfizer-BioNTech COVID-19 vaccines, were in line with what was mentioned above. In addition, rare events that included Bell's palsy and lymph node swelling were also documented [14]. Reports among the American population likewise demonstrated similar side effects after Pfizer-BioNTech and Moderna COVID-19 vaccines, with rare cases of anaphylaxis [15]. The recorded side effects after the first dose of Pfizer-BioNTech COVID-19 vaccine also included a case of neurological complication (Guillain-Barre Syndrome) [16], and anaphylaxis [12]. Rare events following the Oxford–AstraZeneca vaccine also included thrombotic adverse reactions [17-19]. Reports also proposed a possible association between COVID-19 vaccines and cardiovascular adverse events [20-22].

Prior research suggests that age might be an important determinant for the occurrence of the side effects after vaccination. Older adults were found to have mild to moderate side effects due to the Moderna vaccine [23]. Similarly, a study on the Pfizer-BioNTech COVID-19 vaccine reported that people less than 60 years old had more frequent flu-like symptoms compared to 60 years and older [14]. Another investigation suggests a comparable safety profile between younger and adults, however, lower reactogenicity was observed in older adults, with no occurrence of severe side effects in adults ≥60 years [12]. Reports from a randomized, double-blind, placebo-controlled, phase 2 trial on an adenovirus 5 vector-based vaccine showed that adults aged 18–54 years had increased reactogenicity after a single dose in comparison to adults aged 55 years and older [10]. Comparably, Baden *et al*. observed that the side effects after the Moderna vaccine were more frequent in the 18 to <65 years old group than the ≥65 years old group [24]. In real-world practice, the Sinopharm vaccine showed side effects that were more frequent in ≤ 49-year-old [13].

Generally, side effects represent a major determinant of vaccination acceptance. With the newly developed vaccines, there is a growing need for more investigations, in real practice, on the side effects of the COVIS-19 vaccine. With this growing need, the current study was performed to investigate the side effects after the first dose of the Oxford–AstraZeneca vaccine among vaccine recipients at King Abdullah bin Abdulaziz University Hospital (KAAUH), Riyadh, Saudi Arabia. A particular emphasis was how age affects the frequency and the severity of the side effects during the three days post-vaccination.

Materials and Methods

Study design, setting, and participants

A cross-sectional survey was conducted to collect data from individuals (≥ 18 years old) who took the first dose of the Oxford–AstraZeneca COVID-19 vaccine at KAAUH, Riyadh, Saudi Arabia. The target individuals were those who received the first dose of the Oxford–AstraZeneca COVID-19 vaccine at KAAUH from February 28 – March 12, 2021. A convenient sampling technique was used, and the data was collected through a telephone-based survey. During the two-week study period, two of the investigators approached the vaccine recipients on the third day after receiving the vaccine and invited them to take part in the study. The investigators used the hospital telephone number to contact the vaccine recipients.

The appropriate sample size was calculated based on the general rule of having a minimum of five observations per variable, and acceptable sample size would have 10 observations per variable [25]. The survey consisted of 40 variables and hence the required sample size was 400. However, the investigators aimed to collect as many responses as possible from the vaccine recipients during the study period.

Study instrument

A telephone-based survey was used to collect data from the vaccine recipients. The survey was developed based on the previously published literature and the side effects of the vaccines announced on the websites of the World Health Organization and Centers for Disease Control and Prevention. The survey involved two sections. The first section encompassed demographic characteristics which included age, weight, height, gender, ethnicity, co-morbid conditions, and previous exposure to COVID-19 disease. The second section asked about the symptoms experienced in the first three days post-vaccination. A list of ten symptoms was provided which comprised fever, sore through, myalgia, eye muscle pain, loss of smell or taste, shortness of breath, headache, numbness, palpitation, and gastrointestinal symptoms. The participants were also asked to add any additional symptoms that they experienced and they were not mentioned in the list. Furthermore, the participants were requested to rate the severity of each symptom as mild, moderate, or severe. Two additional questions in the second section examined the onset and duration of the side effects, and the use of painkillers to monitor some conditions.

The survey underwent content validity by a physician, a clinical pharmacist, an infection control nurse from KAAUH, and an assistant professor from the College of Pharmacy, Princess Nourah University. Besides, face validity was judged by administering the survey to six vaccine recipients. The survey was piloted on 15 vaccine recipients to test the study feasibility before large-scale data collection. The final data analysis excluded the pilot study results.

Ethical considerations

This study was approved by KAUUH Institutional Review Board (IRB Log #: H-01-R-059). Participants gave their consent in an

electronic form before participating in the study. Participants were informed that their participation was voluntary and they could drop out of the study at any time without any effect on their relationship with KAAUH. Additionally, subjects were assured that their identity would be confidential and the recorded information would be kept secure.

Data analysis

Data analysis was performed using Statistical Package for Social Sciences (IBM SPSS – version 24). Descriptive statistics were performed in the form of frequency and percentage. For categorical data, the Chi-square ($\chi 2$) test/ Fisher exact test was used, as appropriate, to report any associations between independent and dependent variables. Quantitative data were checked for normal distribution and compared using a t-test. The data was then presented as a mean with standard deviation. A P-value of < 0.05 was considered in this study.

Results and Discussion

Characteristics of the participants

During the study period, 528 vaccine recipients answered the survey. Participants were asked about their age, BMI, previous COVID-19 disease, and comorbidities. The results of this section are presented in **(Table 1)**.

Table 1. Characteristics of the participants (N = 528)

Variable	Outcome, n (%)		P-value*
	≤50 (n = 409)	>50 (n = 119)	
Gender			
Male	190 (46.5)	73 (61.3)	0.004**
Female	219 (53.5)	46 (38.7)	
BMI			
Under weight	24 (6.3)	5 (4.9)	0.46
Normal weight	147 (38.3)	35 (34.3)	
Over weight	115 (29.9)	28 (27.5)	
Obese	98 (25.5)	34 (33.3)	
Previous COVID-19 infection	32 (7.8)	4 (8.1)	0.089
Comorbidities			
Heart disease	2 (0.5)	11 (9.2)	0.00*
Immune disease	3 (0.7)	1 (0.8)	0.9
Lung disease	21 (5.1)	9 (7.6)	0.3
Hypertension	18 (4.4)	28 (23.5)	0.00**
Diabetes mellitus	14 (3.4)	23 (19.3)	0.00**

*Chi-square test or Fisher's Exact test were used as appropriate.
** Indicates significantly different characteristics.
Abbreviations: SD, Standard Deviation; BMI, Body Mass Index.

Side effects reported after receiving the first dose of the Oxford–AstraZeneca vaccine

Study participants were asked about the side effects they experienced during the three days post-vaccination. The findings of this part, according to age groups, are illustrated in **(Table 2)**. Amongst all participants, the commonly experienced side effects during the first day were; myalgia (49.8%), fever (42%), and headache (40%). Less frequent side effects involved numbness (8.5%), eye muscle pain (6.3%), palpitations (4.7%), shortness of breath (4.4%), sore throat (4.2%), gastrointestinal symptoms (4.2%), and smell or taste loss (1%). No anaphylaxis or thrombotic events were reported during the study period.

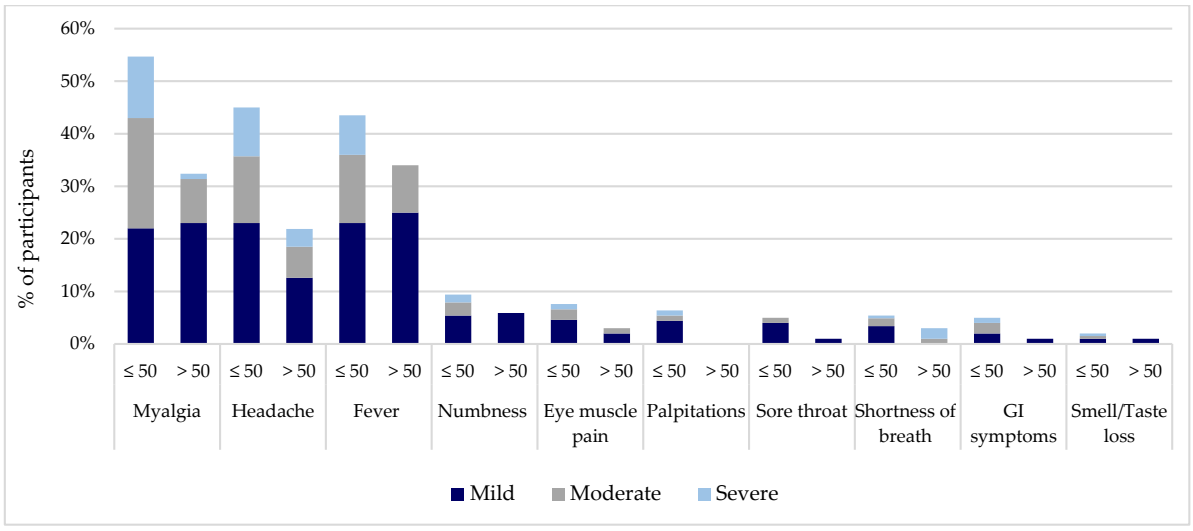
Table 2. Side effects to COVID-19 vaccine reported within three days after receiving the first dose of the Oxford–AstraZeneca vaccine

Side effect	Outcome, n (%)		P-value*
	≤50	>50	
Day 1			
Myalgia	225 (55.0)	38 (31.9)	0.00**
Headache	185 (45.2)	26 (21.8)	0.00**
Fever	181(44.3)	41 (34.5)	0.05
Numbness	38 (9.3)	7 (5.9)	0.24
Eye Muscle Pain	30 (7.3)	3 (2.5)	0.05
Smell/Taste Loss	3 (.7)	1 (.8)	0.82
Palpitation	25 (6.1)	0 (0)	0.006**
Sore Throat	21(5.1)	1 (.8)	0.03***
Shortness of breath	21(5.1)	2 (1.7)	0.10
Gastrointestinal symptoms	21(5.1)	1(.8)	0.039*
Day 2			
Myalgia	198(48.4)	18(15.1)	0.00**
Headache	141 (34.5)	13 (10.9)	0.00**
Fever	147(35.9)	18(15.1)	0.00**
Numbness	25 (6.1)	2 (1.7)	0.05
Eye Muscle Pain	32 (7.8)	0 (0)	0.00**
Smell/Taste Loss	7 (1.7)	0 (0)	0.15
Palpitation	19 (4.6)	1 (0.8)	0.05
Sore Throat	18 (4.4)	0(0)	0.02**
Shortness of breath	13 (3.2)	2 (1.7)	0.38
Gastrointestinal symptoms	21 (5.1)	0 (0)	0.01**
Day 3			
Myalgia	92 (22.5)	4 (3.4)	0.000**
Headache	70 (17.1)	3 (2.5)	0.000**
Fever	47 (11.5)	2 (1.7)	0.001**
Numbness	12 (2.9)	1 (0.8)	0.195
Eye Muscle Pain	12 (2.9)	0(0)	0.059
Smell/Taste Loss	2 (0.5)	0(0)	0.445
Palpitation	14 (3.4)	0 (0)	0.041**
Sore Throat	10 (2.4)	1(0.8)	0.281
Shortness of breath	8(2.0)	3(2.5)	0.704
Gastrointestinal symptoms	16 (3.9)	0 (0)	0.028**

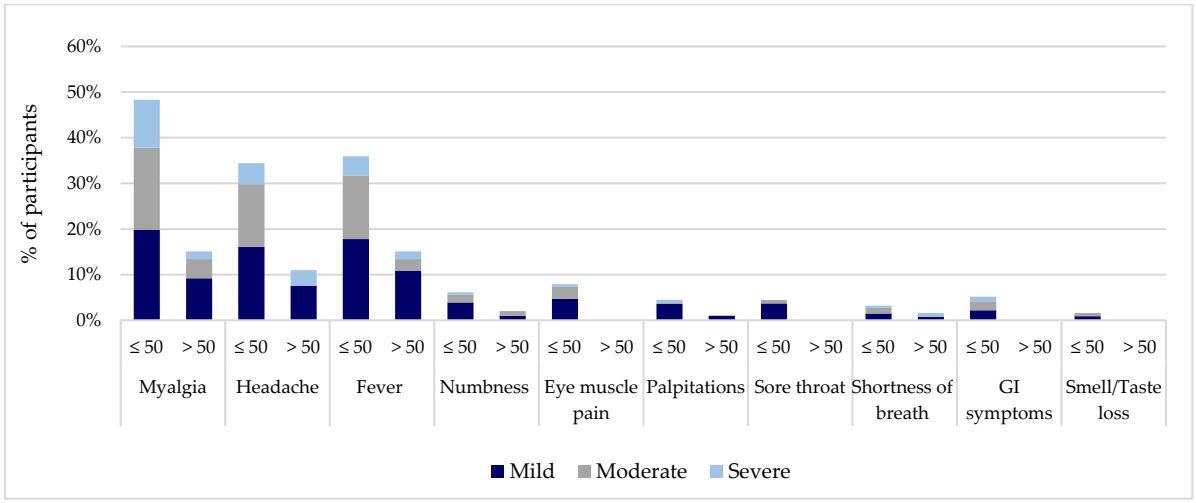
*Chi-square test or Fisher's Exact test were used as appropriate
** Indicates significant difference

The severity of the side effects reported after receiving the first dose of the Oxford–AstraZeneca vaccine (according to the age group)

The survey also investigated the severity of the side effects as perceived by the participants during the three days following vaccination. Responses to this inquiry are shown in **(Figure 1)**.



a)



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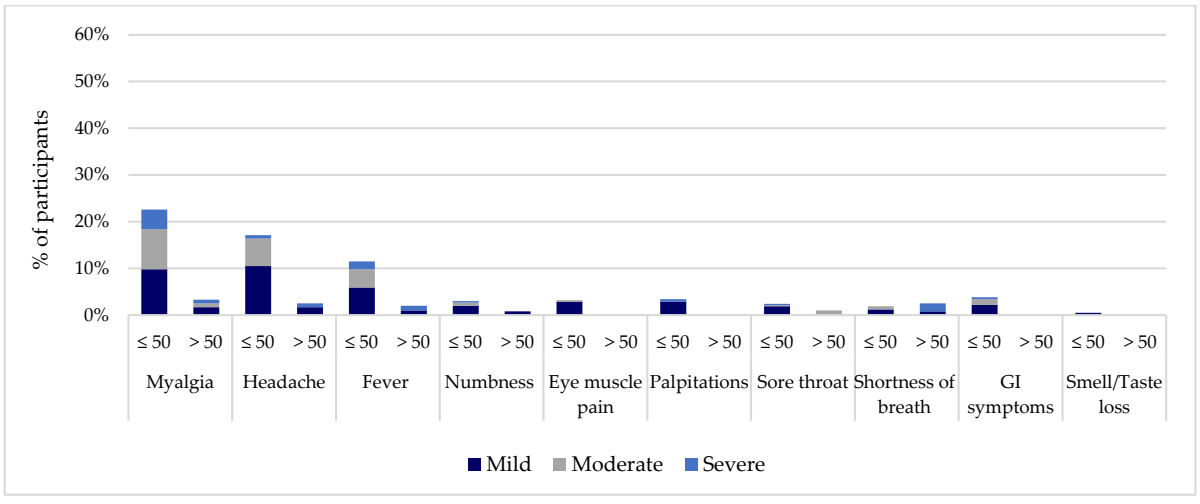

c)

Figure 1. Severity of side effects reported by participants (%) during (A). day 1, (B). day 2, and (C). day 3 post-vaccination (n = 409 for ≤ 50, n = 119 for > 50)

Onset and duration of the side effects after receiving the first dose of the Oxford–AstraZeneca vaccine

Of interest to this study was also the onset and the duration of the side effects reported among the two age groups. The findings of this part are illustrated in **(Table 3)**.

Table 3. Onset and duration of the side effects reported among the two age groups (n = 528)

Variable	<50 (n = 409)	>50 (n = 119)	P-value*
Onset of side effects in hours, n (%)			
<12	124 (47.1)	32 (26.9)	0.00**
12-24	48 (18.3)	43 (36.1)	
>24	91 (34.6)	44 (36.9)	
Duration of side effects in hours, (mean±SD)	37 ±19.5	32 ±13.6	0.0671
Symptoms relieved by painkillers, n (%)			
Yes	281 (69)	68 (57.1)	NA
No	12 (2.9)	1 (0.8)	
Not Taken	88 (21.6)	50 (42)	
Not sure	26 (6.4)	0 (0)	

*Chi-square test or student's t-test were used as appropriate
** Indicates significant difference
NA indicates that the comparison test is not applicable.

This study compared the side effects between two age groups (≤ 50-year-old versus > 50-year-old) following administration of the first dose of the Oxford–AstraZeneca COVID-19 vaccine. The study included 528 participants, of whom 77.5% were in the ≤50-year-old group. Concerning participants' characteristics, the ≤ 50-year-old group appeared to have more females (p-value = 0.004). Heart diseases, hypertension, and diabetes appeared to be more prevalent in the >50-year-old group (p-value is less than 0.05 for all). However, there was no significant difference between the two groups on BMI, immune diseases, lung diseases, or previous COVID-19 infection.

Side effects analysis with a three-day follow-up period after the first dose is provided for all participants. Comparison of the findings with those of other studies confirms that the common side effects were myalgia, headache, and fever [9-11]. Adults aged ≤50 years old showed a higher incidence and intensity of reactions than the >50-year-old group. These findings are consistent with what has been reported in other studies [14, 23, 24] that found increasing age was associated with a reduced frequency and severity of the side effects. In the current study, the ≤50-year-old group showed more frequent side effects which included myalgia, headache, fever, palpitation, sore throat, and gastrointestinal symptoms (p-value is less than 0.05 for all). During the second day, myalgia decreased to approximately 48% in adults aged ≤ 50 years old, compared to approximately 15% in older adults aged 50 years. On the third day, myalgia was reported as an adverse event in 22.5% of adults aged ≤50 years versus 3.4% in adults aged >50 years recipients (3.4%). The decreased frequency of the reported side effects during the first three days was also shown in published research [24]. On day 1, there was no significant difference between the two age groups in the frequency of fever. Whereas, in the next two days, adults aged ≤ 50 years tended to be more vulnerable to fever than older adults aged >50 years, by approximately 47.4% compared to approximately 16.8%. Further analysis showed that the headache in adults aged ≤50 years was decreasing gradually from 45.2% to 34.5%, approaching 17.1% on the third day. In contrast to earlier findings, however, older adults aged >50 years that suffered from the headache within the first two days was approximately 16.35%.

Few participants in both groups had other side effects recorded with more frequency in adults aged ≤50 years compared to the >50-year-old group. Records of the side effects showed clinically significant differences as denoted by p-values less than 0.05: for the first day; sore throat (5% vs. 0.8%), palpation (6% vs. 0 %), and gastrointestinal symptoms (5% vs. 0.8%). Second day; sore throat (4% vs. 0 %), gastrointestinal symptoms (5% vs. 0 %), eye muscle pain (8% vs. 0 %); Third day; palpation (3% vs. 0 %), gastrointestinal symptoms (4% vs. 0 %). Other symptoms e.g.; shortness of breath, smell and taste loss, and numbness were not significantly different between the two groups. In addition, no significant differences were found concerning eye muscle pain on the first and third days. Furthermore, over the next two days, the frequency of the side effects in both groups steadily declined. Additional details are presented in **(Figure 1)**.

The current study also investigated the onset and duration of the side effects. Comparison between the two groups revealed that onset of action was shorter in the ≤50-year-old group (p-value = 0.001). Conversely, there was no significant difference between the two groups concerning the mean duration of the side effects (mean±SD = 37±19.5 vs 32 ±13.6, p-value – 0.067).

The research proposed that older adult's immune response is mostly lower than adults. T cells activation and stimulation decrease with time leading to less response [26]. This might explain the less-prevalent side effects in the older adult group. Moreover, this demonstrates that the prevalence of side effects among adults is higher than in older adults. This also correlates with our findings, in which older adults exhibited less severe symptoms and had less use of painkillers. Nevertheless, further research to support observations of age-related factors and symptoms reporting is needed.

The use of painkillers appeared to improve the symptoms that can be managed by this class of medications. Furthermore, the investigators found no serious side effects that might be linked to the vaccine.

Conclusion

This study concluded that the COVID-19 vaccine was safe and well-tolerated. The ≤50-year-old group was more prone to side effects compared to the >50-year-old group. Further studies are still needed to more establish such an observation.

Limitations

The findings presented in the current study should be understood in light of some limitations the study has. Participants were subjected to recall bias because the data was collected on the third day following vaccination. Concerning the severity of the side effects, a subjective scale (mild, moderate, or severe) was used to determine the severity of symptoms; a more objective criterion might have resulted in some variation in participants' responses. Furthermore, more females were in the age group ≤50-year-old, and gender might affect the interpretation of the findings. As well, the study is a single center. Consequently, the findings might not be generalized to other settings.

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Conflict of interest: None

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Ethics statement: The participants received information about the study. Informed consent was obtained from the participants before taking part in the study.

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