JJBS

Volume 18, Number 2,June 2025
ISSN 1995-6673
Pages 197 – 209
https://doi.org/10.54319/jjbs/180201

Jordan Journal of Biological Sciences

Short-term and Long-term Adverse Effects of COVID-19 Vaccines and its Associated Factors: A Cross-sectional Study from Jordan

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Received: May 23, 2024; Revised: August 26, 2024; Accepted: October 12, 2024

Abstract

Background: The continual monitoring of COVID-19 vaccine safety is a complex process that requires further investigation. This study aims to investigate the occurrence of adverse effects reported by adult Jordanian individuals who have received a minimum of one dose of the locally available COVID-19 vaccines. Methods: Participants were recruited from multiple sources (hospitals, centers, laboratories, universities, and general community) to complete a validated questionnaire of three sections: socio-demographics, vaccination status and potential short-term (STSE) and long-term adverse effects (LTSE) of vaccinations. Results: A total of 1047 participants were enrolled in this study with a mean age of (33.44±15.72 years) and (52.8%) were female participants. The mean duration between the first dose and the time of filling the questionnaire was 507.46±131.87 days. Pfizer-BioNTech, Sinopharm, and AstraZeneca vaccines were most administered with two or more doses (94.8%). Of total participants, 58.5% reported at least one STSE with fatigue being the predominant (37.1%). All study subjects reported at least one LTSE, with fatigue (N=402, 38.4%) being the most frequently reported, followed by decreased concentration (N=343, 32.8%) and mood disturbances (N=333, 31.8%). Older age, male gender, smoking, chronic co-morbidities, multiple COVID-19 infections, and COVID-19 vaccine type and number of doses were significantly associated with many STSE and LTSE ($P<0.05$). Sinopharm vaccine recipients had a significantly higher frequency of most LTSE, whereas AstraZeneca vaccine recipients had a significantly higher frequency of most STSE. Conclusion: The frequency of COVID-19 vaccines LTSE was reported. Most reported adverse effects are mild confirming the risk-benefit value of COVID-19 vaccines.

Keywords*:* adverse effects, AstraZeneca, COVID-19 vaccines, long-term, Pfizer-BioNTech, Sinopharm

1. Introduction

After the flu of 1918, COVID-19 has been recognized as the fifth pandemic (Liu *et al*., 2020a). Since it was first discovered in Wuhan, China in October 2019, COVID-19 quickly spread worldwide (Liu *et al*., 2020a). As of July 2024, 775 million people have been infected with COVID-19 and over 6 million have died globally (WHO 2024). Since the genetic code of SARS-CoV-2 was revealed, global vaccine companies and scientists have started a race toward vaccine development that the entire world depends on (Haidere *et al*., 2021). The best method for limiting the pandemic is vaccination in conjunction with infection prevention (Haidere *et al*., 2021).

Several different potential vaccines have been developed for COVID-19, including inactivated or weakened virus vaccines, protein-based vaccines, viral vector vaccines and RNA and DNA vaccines (WHO 2023). By July 2021, 322 vaccines have been proposed, of which 99 were tested in clinical trials, 25 have reached phase III efficacy studies and 18 have received approval based on reported efficacies of their vaccines (Tregoning *et al*., 2021). The most utilized vaccines around the globe are Pfizer–BioNTech, Moderna, AstraZeneca–University of Oxford, Johnson & Johnson, Sputnik V, Sinovac Biotech, Sinopharm, Novavax and Bharat Biotech (Tregoning *et al*., 2021).

Many COVID-19 vaccines were approved and used in Jordan including Pfizer-BioNTech, AstraZeneca, Sinopharm and Sputnik V (Qaqish *et al*., 2022). As of 2023, more than 10 million doses of COVID-19 vaccines have been administered in Jordan with Pfizer-BioNTech and Sinopharm being the most commonly used vaccines

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(MOH 2023a, MOH 2023b). In the Middle East region, different COVID-19 vaccines were available in different countries with Pfizer-BioNTech and Sinopharm being the most common (Bizri *et al*., 2023). Pfizer-BioNTech was widely used in Saudi Arabia, United Arab Emirates, Qatar and Kuwait while Sinopharm was commonly used in United Arab Emirates and Bahrain (Ganesan *et al*., 2022; Bizri *et al*., 2023).

Most vaccinations, compared to placebo, lower the percentage of participants having confirmed symptoms of COVID-19, and, for some, there is strong evidence that they lower severe or critical disease (Graña *et al*., 2022). In comparison to a placebo, Pfizer-BioNTech, Moderna, AstraZeneca, Sinopharm, and Bharat Biotech all showed lower incidences of symptomatic COVID-19 with vaccine effectiveness (VE): 97.84%, 93.20%, 70.23%, 78.10% and 77.80%, respectively. There is high-certainty evidence that Pfizer-BioNTech, Moderna, Janssen (Ad26.COV2.S) and Bharat Biotech vaccines largely reduced the incidence of critical or severe disease from COVID-19 with efficacies of: 95.70%, 98.20%, 76.30% and 93.40%, respectively (Graña *et al*., 2022).

Numerous studies reported the immediate or short-term adverse effects (STSE) of COVID-19 vaccinations. Data on the long-term or delayed effects of vaccinations are still lacking. The public and the scientific community must have access to these studies. Most significantly, safety data must be offered in a transparent and evidence-based approach (Dar-Odeh *et al*., 2022).

It is critical to continuously monitor COVID-19 vaccine adverse effects, and studies are now being conducted to monitor vaccination safety. So far, no vaccine can be labeled completely free of adverse effects, but most of these adverse effects are preventable or treatable (Spencer *et al*., 2017). Early adverse effects have been reported after all types of vaccines but are more likely to occur after the new-generation vaccines (Abu-Halaweh *et al*., 2021). The most common adverse effect reported shortly after the first two doses was pain at the injection site, followed by fatigue, headache and myalgia (Mulligan *et al*., 2020; Ganesan *et al*., 2022). About one in six recipients of the COVID-19 vaccine may complain of long-term adverse effects (LTSE) (Dar-Odeh *et al*., 2022). The most frequently reported LTSE was fatigue and its related symptoms. Among COVID-19 vaccines Pfizer-BioNTech was the least associated with LTSE (Dar-Odeh *et al*., 2022).

In this study, we aim to compare LTSE associated with COVID-19 vaccines and explore the potential effect of gender, age, co-morbidities and vaccine type or number of doses on the development of these adverse effects.

2. Methods

2.1. Study Design

A cross-sectional observational design was implemented in this study. The sample population consisted of adult Jordanian individuals who were eighteen years of age or older and had received at least one dose of any of the locally available COVID-19 vaccines, including Pfizer-BioNTech (Pfizer, United States of America and BioNTech, Germany, COMIRNATY®), Sinopharm (Sinopharm China National Biotec Group, China, BBIP-CorV), AstraZeneca (Oxford University, United Kingdom and AstraZeneca, United Kingdom/Sweden, ChAdOx1-S), Sputnik (Gamaleya Research Institute of Epidemiology and Microbiology, Russia, Gam-COVID-Vac), Moderna (Moderna, USA, Spikevax), and Johnson & Johnson (Janssen Pharmaceutical Company of Johnson & Johnson, USA, Janssen).

2.2. Data Collection

Data was collected through the use of an online survey administered via the Google Forms platform and disseminated to participants through various channels, including personal interviews, university lectures, patient encounters and social media platforms. The survey was accessible for four months, starting from July 28th to November 28th, 2022. The mean duration between the first dose and the time of filling the questionnaire was about (507.46 days ± 131.87 days). The final sample size of the study consisted of 1047 individuals. Participants were recruited from multiple sources, including university students from four public and private institutions, inpatients and outpatients from three public and private hospitals, visitors to private and public tertiary care centers and clinics, visitors to private and public diagnostic laboratories, family members and friends of participants, and members of the community at large. The study population was diverse, with representation from different geographic regions, age groups, genders, and socio-economic statuses, as well as individuals with varying degrees of health.

The online questionnaire, available exclusively in the Arabic language, consisted of 45 questions that were divided into three sections: socio-demographics, vaccination status, and potential STSE and LTSE of the vaccine. The socio-demographic section comprised questions regarding gender, age, height, weight, co-morbidities, smoking status, and history of COVID-19 infection. The vaccination status section included questions about the number of doses received, type of vaccine, timing of doses, and immediate adverse effects after vaccination. The adverse effects section was further divided into sub-sections about different organ systems, including the neurological, cardio-vascular, respiratory, gastrointestinal, reproductive, musculoskeletal, integumentary, endocrine systems, as well as systemic signs and symptoms. Each sub-section focused on specific symptoms related to the respective organ system. Participants responded to the questions with yes or no. Body mass index (BMI) was calculated using weight in kilograms divided by height in meters squared. Adverse effects that occurred within 7 days post vaccination were considered STSE, while adverse effects after 7 days of vaccination were considered LTSE.

The questionnaire items pertaining to the STSE and LTSE of COVID-19 vaccines were chosen following a comprehensive review of the scientific literature that encompassed case reports, cross-sectional studies, clinical trials, systematic reviews, and meta-analyses, as well as other relevant studies that have documented vaccine adverse effects (Alqassieh *et al*., 2021; Dar-Odeh *et al*., 2022; Bhandari *et al*., 2022; Bhattacharya *et al*., 2022; Dawoud *et al*., 2022; Ilonze and Guglin, 2022; Medeiros *et al*., 2022). Furthermore, we consulted official reports from local regulatory bodies, such as the Jordanian Ministry of

Health (MOH 2023a), the Jordan Food and Drug Administration (JFDA 2023), and the Jordanian Center for Disease Control (JCDC 2023), to identify any available data on reported vaccine adverse effects. The opinions of specialized healthcare professionals were also sought to incorporate adverse effects reported within the community. In addition, a pilot test of the survey was conducted on 5 participants, and necessary modifications were made to the questionnaire before it was made available to the study participants. Participants were provided with a clear explanation of the purpose of the study and a guarantee of confidentiality prior to their participation, for which they were required to provide virtual consent.

2.3. Ethical Approval

The study was granted ethical approval by the institutional review board (IRB) at the Hashemite University (Reference No.22/4/2021/2022). To protect the participants' privacy, no personal information was included in the survey. Participants were given the option to withdraw from the study at any time without the need to provide an explanation. The data collected was assigned codes based on the national identification numbers of the participants, serving as deidentifiers. The collected data was used solely for statistical analysis purposes.

2.4. Statistical Analysis

The statistical analysis was conducted with the use of SPSS software (Statistical Package for the Social Sciences version 24.0 Chicago, IL, USA). Categorical variables were presented as numbers and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Moreover, continuous variables, such as age and BMI, were stratified into age groups of 20 years or categorized as underweight, normal weight, overweight, or obese for BMI. The differences in baseline characteristics between vaccine types and number of doses were evaluated using the Chi-squared test or Fisher's exact test, as appropriate. Similarly, the Chi-squared test was utilized to compare the frequency of adverse reactions among different vaccine types and doses, and bivariate Pearson correlation was applied to confirm the results of the Chi-squared test, when applicable. Statistical significance was established at $P < 0.05$. Adverse effects that occurred with a frequency of less than 5% were excluded from inferential statistical analysis. Moreover, multivariate analysis was performed using binary logistic regression.

3. Results

3.1. Participants (Demographics)

A total of 1047 participants who received at least one of the vaccines Pfizer-BioNTech, Sinopharm, AstraZeneca, Moderna, Johnson and Johnson, and Sputnik vaccines concluded the sample of the study, with Pfizer-BioNTech being the majority 617 (58.9%). The demographic distribution of the selected individuals is shown in Table 1. Participants were 494 (47.2%) males and 553 (52.8%) females. The mean age was 33.44 ± 15.72 years, with the majority of the participants ages range between 20–60 years (69.1%). Most participants were non-smokers (N = 703, 67.1%) and only 376 (35.9%) had chronic diseases with hypertension (16.3%) and diabetes (12.3%) being the most frequent chronic diseases respectively (Table 1). The average BMI was 25.6 ± 5.3.

Table 1. Demographic, clinical data and COVID-19 infection and vaccination details of the study population (N = 1047).

	Variable		Number (%)	
Age (Years)	0-20		188 (18.0)	
	21-40		475 (45.4)	
	41-60		248 (23.7)	
	Above 60		136 (13.0)	
Gender	Male		494 (47.2)	
	Female		553 (52.8)	
BMI	Underweight <18.5		47 (4.5)	
	Normal 18.5-24.9		407 (38.9)	
	Overweight 25-29.9		390 (37.2)	
	Obese ≥30		203 (19.4)	
Smoking	Yes		344 (32.9)	
	No		703 (67.1)	
Chronic diseases	Yes		376 (35.9)	
	Hypertension		171 (16.3)	
	Diabetes Mellitus		129 (12.3)	
	Cardiac diseases		70 (6.7)	
	Hyperlipidemia		66 (6.3)	
	Thyroid diseases		61 (5.8)	
	Asthma		57 (5.4)	
	Others (cancer, kidney, digestive, lung disease, etc)		94 (9.0)	
COVID-19 Infection	Yes		573 (54.7)	
	Confirmed by RT-PCR		432 (41.3)	
	One		374 (35.7)	
	Two		150 (14.3)	
	Three		36 (3.4)	
	Four		13 (1.2)	
	After vaccine		354 (33.8)	
	Before vaccine		219 (20.9)	
COVID-19 Vaccination	Yes		1047 (100)	
	One dose		54 (5.2)	
	Two doses		733 (70.0)	
	Three doses		244 (23.3)	
	Four doses		16 (1.5)	
Type of vaccine	First dose	Second dose	Third dose	Forth dose
Sinopharm	329 (31.4)	320 (30.6)	22 (2.1)	2 (0.2)
Pfizer	617 (58.9)	592 (56.5)	235 (22.4)	14 (1.3)
Johnson	1 (0.1)	0 (0.0)	1 (0.1)	0 (0)
Moderna	2 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
AstraZeneca	88 (8.4)	74 (7.1)	0 (0)	0 (0)
Sputnik V	10 (1.0)	6 (.6)	0 (0)	0 (0)
Duration/days	First dose	Second dose	Third dose	
0-100	1 (0.1)	10 (1.0)	9 (0.9)	
101-200	27 (2.6)	51 (4.9)	18 (1.7)	
201-300	59 (5.6)	61 (5.8)	58 (5.5)	
301-400	83 (7.9)	119 (11.4)	101 (9.6)	
401-500	252 (24.1)	290 (27.7)	19 (1.8)	
Above 500	599 (57.2)	432 (41.3)	16 (1.5)	

3.2. Participants (COVID-19 infection and vaccination)

Out of all participants, only 573 (54.7%) reported COVID-19 infection, 75% of these infections were confirmed by Reverse transcription polymerase chain reaction (RT-PCR). While the majority of these had only one infection (N = 374, 65.3%), others had two (N =150, 26.2%), three (N = 36, 6.3%), and even some had four (N = 13, 2.3%) infections (Table 1). Participants who reported COVID-19 infection before any dose of vaccination were 219 (38.2%), while who got infected after receiving at least one dose of the vaccine were 354 (61.8%). Regarding

vaccination, 94.8% of the participants received at least two doses of the vaccine.

3.3. Reported STSE after vaccine administration

As demonstrated in Table 2, a total of 613 (58.5%) participants reported at least one STSE post-vaccination. Fatigue (37.1%) was the predominant STSE, followed by myalgia, fever, redness and pain at the site of infection, headache, arthralgia, and palpitation respectively. The frequency of reported STSE was almost the same after each dose of vaccination (Figure 1A, B and C) with no participants receiving a booster dose (third dose) of AstraZeneca vaccine (Figure 1C and Table 1). However, participants who received AstraZeneca had significantly higher percentages of almost all STSE (Figure 1 and Table 3). Sinopharm-vaccinated participants were significantly the least to report STSE post-vaccination (Figure 1 and Table 3). Of notice is that the first and the second doses were of the same vaccine type for most participants while the third dose were of a different vaccine type.

The number of vaccines doses each participant received showed significant association with age, gender, BMI, chronic diseases and COVID-19 infections (Table 3). Furthermore, despite no significant association with STSE in general, there was a significant association with fatigue, myalgia, fever, and headache as the frequency of these adverse effects increased with the second dose compared to the first dose and then dropped slightly with the third dose (Figure 2 and Table 3).

3.4. Reported LTSE after vaccine administration

All participants reported at least one LTSE (N = 1047). The most frequent LTSE reported as shown in Table 2 was fatigue (38.4%), followed by decreased concentration levels and mood changes being the second and third most frequent adverse effects respectively. Moreover, out of 553 female participants, 138(24.7%) reported irregularities in the menstrual period. Jaundice (1.9%) and bloody urine (1.6%) were the least reported LTSE. Participants who received third dose of Sinopharm were significantly the most to report all LTSE except menstrual irregularities, urinary frequency, change in libido, and change in bowel habits that were not statistically significant (Figure 3C and Table 3).

Fatigue-associated symptoms (headache, myalgia, muscle weakness) as well as most LTSE demonstrated in Table 3 had statistically significant associations with the number of vaccine doses participants got. However, menstrual irregularities, urinary frequency, and change in libido were not statistically significant. Interestingly, some LTSE frequencies either significantly increased with the second dose and then dropped with the third dose (fatigue, headache, loss of concentration, mood changes, muscle weakness or pain, difficulty of breathing and palpitation), or there was a gradual decrease of the frequencies of other LTSE with increased number of doses (Figure 4).

Table 2. Frequency of short-term (STSE) and long-term adverse effects (LTSE) of COVID-19 vaccines reported by study participants (N = 1047).

	Variable	Number (%)
Short-term adverse effects (STSE)	Yes	613 (58.5)
	Fatigue	388 (37.1)
	Myalgia	299 (28.6)
	Fever	291 (27.8)
	Redness and pain at injection site	272 (26.0)
	Headache	240 (22.9)
	Arthralgia	175 (16.7)
	Palpitation	51 (4.9)
Pregnancy or abortion during vaccination	Yes	11 (1.1)
	Normal pregnancy	6 (0.6)
	Abortion	5 (0.5)
Long-term adverse effects (LTSE)	Yes at least one	1047 (100)
	Any diagnosis after vaccination	54 (5.2)
	Clotting	8 (0.8)
	Lung disease	5 (0.5)
	Joint disease	12 (1.1)
	Other disease	29 (2.8)
	Increase in previous diseases after vaccine	102 (9.7)
	Fatigue	402 (38.4)
	Loss of concentration	343 (32.8)
	Mood changes	333 (31.8)
	Muscle weakness or pain	287 (27.4)
	Headache	276 (26.4)
	Menstrual period changes (females only)	138 (24.7)
	Dizziness	237 (22.6)
	Numbness and paraesthesia	234 (22.3)
	Change in weight	219 (20.9)
	Increased weight	122 (11.7)
	Decreased weight	97 (97)
	Anemia symptoms	185 (17.7)
	Hotness or cold	177 (16.9)
	Feeling cold	96 (9.2)
	Feeling hot	81 (7.7)
	Difficulty of breathing	166 (15.9)
	Joints pain	158 (15.1)
	Chest pain	150 (14.3)
	Palpitation	147 (14.0)
	Abdominal distension	139 (13.3)
	Thirst	131 (12.5)
	Urinary frequency	119 (11.4)
	Changes in bowel habits	108 (10.3)
	Constipation	60 (5.7)
	Diarrhea	34 (3.2)
	Bloody stool	14 (1.3)
	Changes in libido (married)	37 (6.8)
	Skin rash	69 (6.6)
	Difficulty in erection (males only)	20 (3.8)
	Difficulty in speaking	32 (3.1)
	Coma or loss of consciousness	28 (2.7)
	Difficulty in conception (married)	28 (2.7)
	Pain or blood during intercourse (females only)	9 (2.0)
	Jaundice	20 (1.9)
	Bloody urine	17 (1.6)

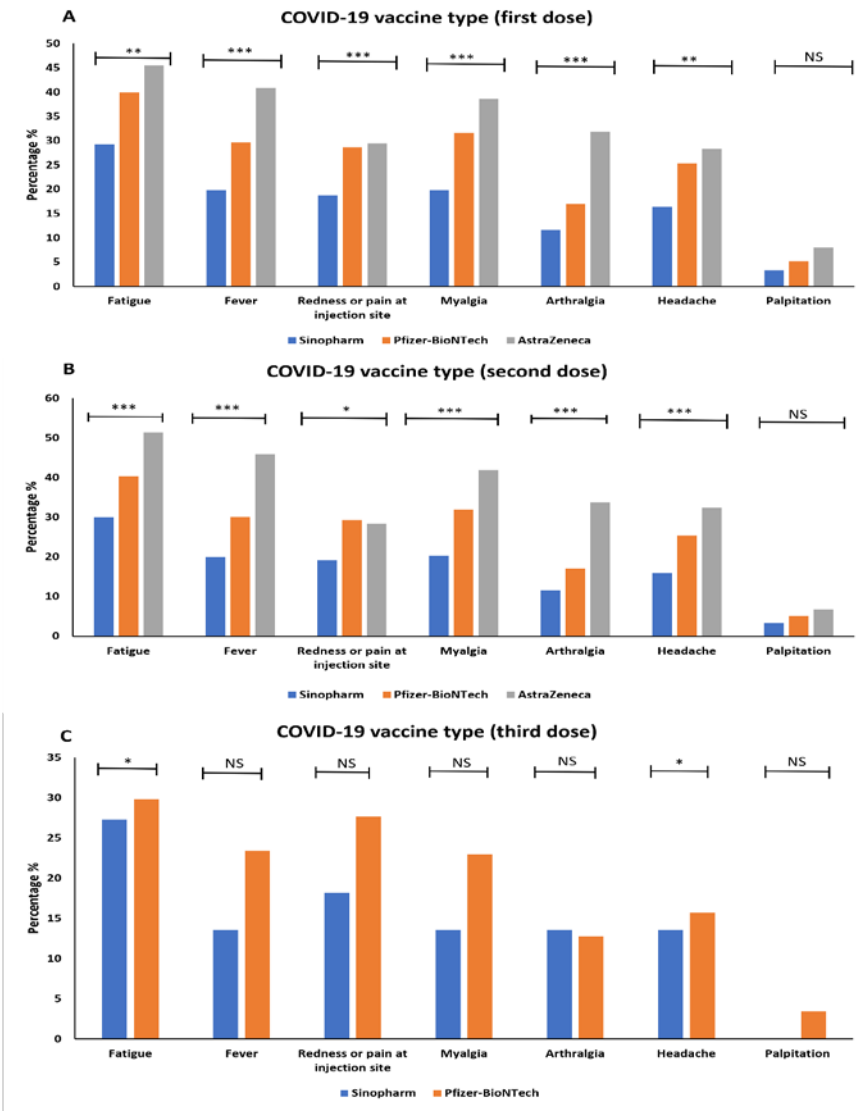

Figure 1. COVID-19 vaccine types and short-term adverse effects (STSE). The frequency of STSE according to COVID-19 vaccine type: first dose (A), second dose (B), and third dose (C). Adverse effects with a frequency less than 5% were not included. *Significance less than 0.05, **Significance less than 0.01, ***Significance less than 0.001, NS not significant

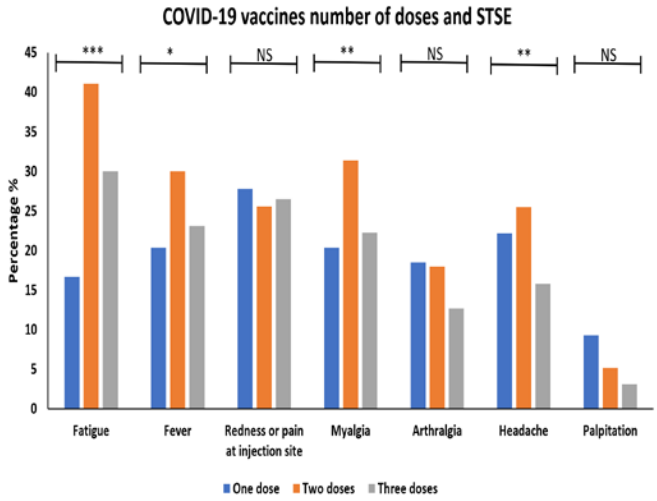

Figure 2. COVID-19 vaccines number of doses and STSE. The frequency of STSE according to COVID-19 vaccine number of doses. Adverse effects with a frequency less than 5% were not included. * Significance less than 0.05, ** Significance less than 0.01, *** Significance less than 0.001, NS not significant.

Table 3. Association of COVID-19 vaccination number of doses (one, two, or three doses) and type of vaccine (Pfizer-BioNTech, Sinopharm, and AstraZeneca) with demographics, COVID-19 infections and COVID-19 vaccination STSE and LTSE. Numbers are for P values estimated by cross tabulation with Chi-square test or Fisher-exact test. Adverse effects less than 5%, COVID-19 vaccines administered less than 5% (Johnson & Johnson, Moderna, and Sputnik), and the fourth dose administered for less than 5% were not included in the analysis.

	Number of vaccine doses	COVID-19 vaccination type (Pfizer-BioNTech, Sinopharm, and AstraZeneca)		
		First dose vaccine type	Second dose vaccine type	Third dose vaccine type
Age	0.000	0.000	0.000	0.000
Gender	0.000	0.258	0.309	0.000
BMI	0.000	0.009	0.001	0.000
Smoking	0.143	0.068	0.072	0.890
Chronic diseases	0.000	0.024	0.108	0.000
COVID-19 infection	0.000	0.129	0.002	0.000
Confirmed RT-PCR	0.001	0.150	0.057	0.005
Timing of infection	0.001	0.101	0.071	0.003
Short-term adverse effects	0.120	0.000	0.000	0.309
Fatigue (short-term)	0.000	0.005	0.000	0.027
Myalgia	0.008	0.000	0.000	0.053
Fever	0.046	0.000	0.000	0.053
Redness and pain at injection site	0.916	0.001	0.021	0.550
Headache (short-term)	0.006	0.004	0.003	0.014
Arthralgia	0.133	0.000	0.000	0.223
Palpitation (short-term)	0.122	0.282	0.341	0.397
Any diagnosis after vaccination	0.089	0.068	0.021	0.562
Increase in previous diseases	0.000	0.003	0.014	0.039
Fatigue (long-term)	0.000	0.288	0.108	0.000
Headache (long-term)	0.000	0.068	0.117	0.000
Loss of concentration	0.001	0.334	0.338	0.002
Mood changes	0.000	0.122	0.390	0.000
Muscle weakness or pain	0.001	0.155	0.392	0.004
Menstrual period changes	0.148	0.336	0.667	0.332
Dizziness	0.000	0.248	0.164	0.000
Numbness and paraesthesia	0.008	0.960	0.684	0.012
Change in weight	0.002	0.710	0.342	0.001
Anemia symptoms	0.000	0.278	0.017	0.000
Hotness or cold	0.000	0.158	0.532	0.000
Difficulty of breathing	0.000	0.134	0.254	0.000
Joints pain	0.028	0.254	0.462	0.017
Chest pain	0.000	0.723	0.166	0.000
Palpitation (long-term)	0.000	0.602	0.441	0.000
Abdominal distention	0.017	0.620	0.870	0.005
Thirst	0.001	0.315	0.030	0.033
Urinary frequency	0.072	0.875	0.911	0.060
Changes in bowel habits	0.004	0.108	0.052	0.086
Changes in libido	0.106	0.104	0.227	0.183
Skin rash	0.009	0.561	0.418	0.034

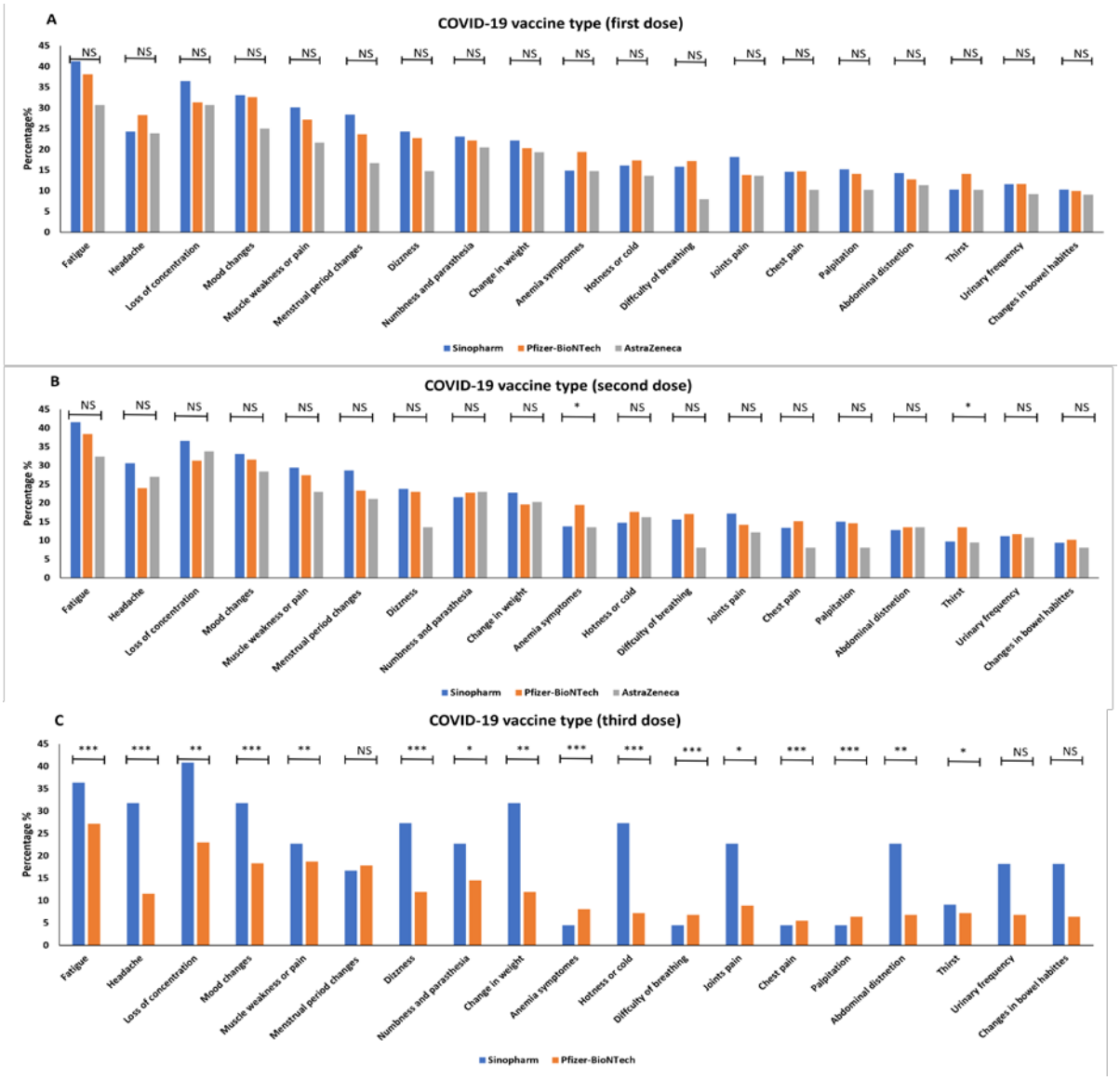

Figure 3. COVID-19 vaccine types and LTSE. (A) COVID-19 vaccine type first dose, (B) second dose, and (C) third dose). Adverse effects with a frequency less than 5% were not included. *Significance less than 0.05, **Significance less than 0.01, ***Significance less than 0.001, NS not significant.

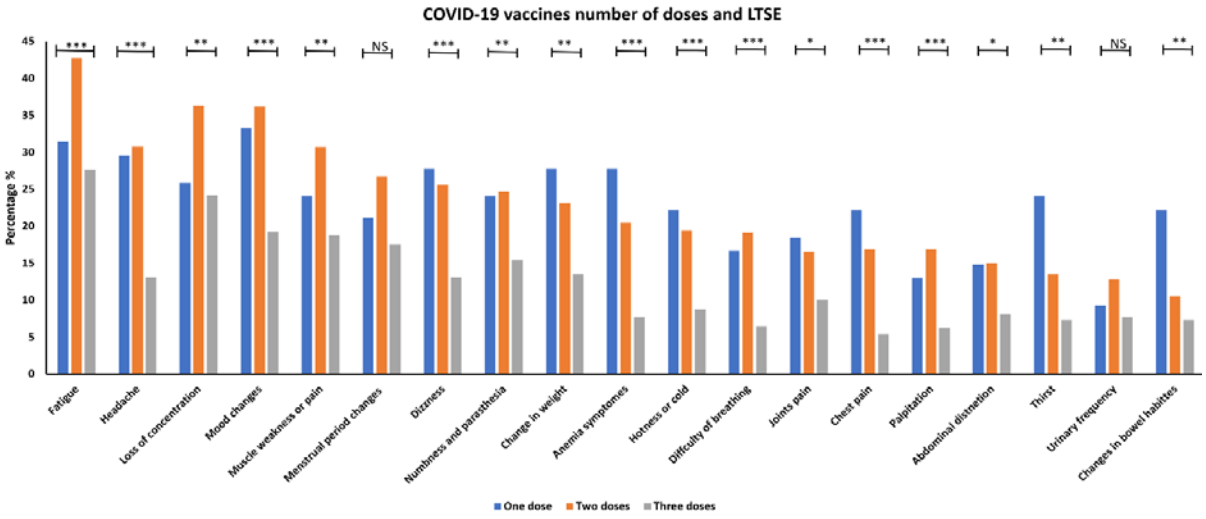

Figure 4. COVID-19 vaccines number of doses and LTSE. Adverse effects with a frequency less than 5% were not included. *Significance less than 0.05, **Significance less than 0.01, ***Significance less than 0.001, NS not significant.

3.5. Factors associated with LTSE

As demonstrated in Table 4, males have a statistically significant association with all of the reported LTSE, but not urinary frequency, which showed no significant association with gender (P > 0.05). Smokers reported more fatigue and urinary frequency in the long-term post-vaccination; however, smoking was not significantly associated with other LTSE. Fatigue had more statistically significant occurrence among males, older age smokers, individuals with chronic diseases, as well as those with multiple COVID-19 infections. Skin rash was not significantly associated with age, obesity, smokers, chronic diseases, or COVID-19 infection. However, skin rash was reported more among males (P = 0.002). Women who reported irregularities in menstrual cycle were associated with older age groups, obesity, chronic diseases as well the number of COVID-19 infections. On the other hand, Males reported more changes in libido.

Table 4. Association of age, gender, BMI, smoking, chronic diseases and COVID-19 infection with COVID-19 vaccine STSE and LTSE. Numbers are for P values estimated by cross tabulation with Chi-square test or Fisher-exact test. Adverse effects less than 5% were not included in the analysis.

	Age	Gender	BMI	Smoking	Chronic diseases	COVID-19 infection
Age	-	0.001	0.000	0.000	0.000	0.000
Gender	0.001	-	0.001	0.000	0.660	0.012
BMI	0.000	0.000	-	0.001	0.000	0.793
Smoking	0.000	0.000	0.001	-	0.301	0.434
Chronic diseases	0.000	0.660	0.000	0.301	-	0.137
COVID-19 Infection	0.000	0.023	0.403	0.101	0.050	-
Confirmed by RT-PCR	0.000	0.011	0.076	0.360	0.021	-
Timing of last infection related to vaccine	0.000	0.019	0.139	0.956	0.000	-
COVID-19 vaccination number of doses	0.000	0.000	0.000	0.143	0.000	0.000
First dose type of vaccine	0.000	0.263	0.009	0.068	0.024	0.129
Second dose type of vaccine	0.000	0.303	0.001	0.070	0.103	0.002
Thrid dose type of vaccine	0.000	0.000	0.000	0.897	0.000	0.000
Short-term adverse effects	0.000	0.000	0.000	0.378	0.008	0.000
Fatigue (short-term)	0.000	0.000	0.000	0.731	0.000	0.000
Myalgia	0.000	0.000	0.000	0.972	0.000	0.000
Fever	0.002	0.000	0.001	0.429	0.517	0.011
Redness and pain at injection site	0.132	0.003	0.044	0.013	0.259	0.005
Headache (short-term)	0.000	0.000	0.000	0.516	0.020	0.000
Arthralgia	0.121	0.000	0.246	0.537	0.237	0.000
Palpitation	0.205	0.000	0.004	0.941	0.838	0.000
Any diagnosis after vaccination	0.192	0.893	0.009	0.118	0.000	0.560
Increase in previous diseases	0.000	0.057	0.004	0.003	0.000	0.025
Fatigue (long-term)	0.000	0.000	0.149	0.031	0.000	0.005
Headache (long-term)	0.000	0.000	0.206	0.066	0.783	0.007
Loss of concentration	0.000	0.000	0.134	0.377	0.699	0.000
Mood changes	0.000	0.000	0.351	0.352	0.305	0.000
Muscle weakness or pain	0.000	0.000	0.401	0.256	0.000	0.000
Menstrual period changes	0.000	-	0.002	0.262	0.001	0.017
Dizziness	0.244	0.000	0.103	0.859	0.004	0.002
Numbness and paraesthesia	0.000	0.000	0.407	0.079	0.000	0.661
Change in weight	0.392	0.000	0.018	0.877	0.006	0.536
Anemia symptoms	0.017	0.000	0.000	0.318	0.441	0.070
Hotness or cold	0.611	0.000	0.052	0.280	0.008	0.072
Difficulty of breathing	0.467	0.000	0.064	0.239	0.000	0.000
Joints pain	0.000	0.004	0.000	0.095	0.000	0.028
Chest pain	0.181	0.000	0.178	0.068	0.000	0.214
Palpitation (long-term)	0.157	0.000	0.179	0.609	0.000	0.018
Abdominal distention	0.377	0.000	0.477	0.220	0.179	0.035
Thirst	1.000	0.003	0.385	0.324	0.033	0.193
Urinary frequency	0.889	0.315	0.365	0.040	0.244	0.011
Changes in bowel habits	0.031	0.015	0.061	0.447	0.000	0.004
Changes in libido	0.100	0.000	0.935	0.412	0.706	0.052
Skin rash	0.522	0.002	0.942	0.859	0.106	0.052

3.6. Multivariate analysis of factors associated with STSE and LTSE

Multivariate regression analysis, shown in Table 5, demonstrates the association between STSE and males, older ages, as well as participants who got infected with COVID-19. Regarding factors associated with LTSE once more, men exhibit statistically significant associations with joint discomfort and weariness. Moreover, males have statistically significant urine frequency (P = 0.038). Smokers are associated with more anemia-related symptoms (P = 0.034) and with muscle pain (P = 0.048). BMI and history of COVID-19 infection of the participants played a minor role, and most LTSE showed no statistically significant association as seen in Table 5. After immunization, individuals' experiences of being hot or chilly were statistically significantly correlated with the number of vaccine doses they had received (P = 0.009). Chronic tiredness, attention loss, and a sense of numbness in the limbs were the most reported symptoms and showed a statistically significant link among subjects who had

received the COVID-19 vaccination the earliest at the time of the interview. Moreover, more of the same people reported an increase in the severity of preexisting chronic illnesses.

Table 5. Multivariate regression analysis of the effect of age, gender, BMI, smoking, chronic diseases, COVID-19 infection and COVID-19 vaccine doses, type and duration on STSE and LTSE. Numbers are for P values estimated by binary logistic regression. Adverse effects less than 5% were not included in the analysis.

	Age	Gender	BMI	Smoking	Chronic diseases	COVID-19 infection	Vaccine doses	Vaccine type	Vaccine duration
Short-term adverse effects (any)	0.015	0.029	0.181	0.130	0.085	0.028	0.566	0.585	0.032
Fatigue (short-term)	0.005	0.278	0.233	0.665	0.158	0.024	0.889	0.954	0.493
Myalgia	0.089	0.202	0.113	0.182	0.250	0.080	0.532	0.780	0.719
Fever	0.094	0.131	0.117	0.116	0.021	0.130	0.540	0.983	0.198
Redness and pain	0.905	0.302	0.617	0.359	0.763	0.621	0.107	0.917	0.250
Headache (short-term)	0.241	0.123	0.331	0.340	0.060	0.132	0.500	0.766	0.716
Arthralgia	0.236	0.069	0.726	0.957	0.014	0.038	0.176	0.672	0.868
Palpitation (short-term)	0.096	0.999	0.130	0.999	0.065	0.824	0.370	0.296	0.316
Any diagnosis after vaccination	0.810	0.486	0.976	0.636	0.577	0.308	0.338	0.172	0.313
Increase in previous diseases	0.862	0.590	0.425	0.636	0.015	0.963	0.513	0.045	0.019
Fatigue (long-term)	0.846	0.028	0.397	0.409	0.022	0.987	0.475	0.182	0.035
Headache	0.899	0.087	0.812	0.444	0.644	0.306	0.564	0.114	0.264
Loss of concentration	0.764	0.950	0.332	0.785	0.768	0.708	0.340	0.233	0.049
Mood changes	0.550	0.232	0.245	0.546	0.485	0.780	0.599	0.928	0.554
Muscle weakness or pain	0.217	0.127	0.554	0.048	0.093	0.916	0.632	0.215	0.719
Menstrual period changes	0.178	0.999	0.156	0.999	0.296	0.235	0.729	0.065	0.388
Dizziness	0.769	0.258	0.824	0.832	0.103	0.527	0.407	0.498	0.113
Numbness and paraesthesia	0.435	0.062	0.300	0.645	0.045	0.127	0.499	0.705	0.025
Change in weight	0.611	0.049	0.080	0.477	0.796	0.580	0.003	0.002	0.839
Anemia symptoms	0.496	0.626	0.343	0.034	0.703	0.636	0.606	0.028	0.107
Hotness or cold	0.283	0.002	0.395	0.922	0.007	0.673	0.009	0.004	0.081
Difficulty of breathing	0.072	0.624	0.367	0.121	0.229	0.912	0.371	0.814	0.015
Joints pain	0.077	0.002	0.400	0.129	0.880	0.162	0.593	0.063	0.062
Chest pain	0.789	0.112	0.424	0.204	0.121	0.737	0.364	0.071	0.452
Palpitation	0.285	0.617	0.762	0.311	0.066	0.143	0.280	0.135	0.834
Abdominal distention	0.473	0.025	0.464	0.125	0.406	0.943	0.137	0.048	0.729
Thirst	0.136	0.283	0.665	0.847	0.654	0.933	0.699	0.242	0.359
Urinary frequency	0.378	0.038	0.916	0.559	0.774	0.960	0.718	0.094	0.751
Changes in bowel habits	0.317	0.133	0.030	0.751	0.302	0.338	0.260	0.447	0.621
Changes in libido	0.062	0.235	0.318	0.272	0.925	0.371	0.474	1.000	0.650
Skin rash	0.918	0.108	0.700	0.985	0.427	0.405	0.533	0.252	0.812

4. Discussion

The adverse reactions to vaccines in general are a globally well-documented issue that mandates appropriate reporting by many authorization and licensing agencies and bodies across the world (Spencer *et al.*, 2017; Dar-Odeh *et al*., 2022; Bhandari *et al*., 2022; JFDA 2023; WHO 2024). Numerous studies reported the STSE of COVID-19 vaccinations (Mulligan *et al*., 2020; Abu-Halaweh *et al*., 2021; Alqassieh *et al*., 2021; Dawoud *et al*., 2022; Ilonze and Guglin, 2022; Medeiros *et al*., 2022). Data on LTSE of COVID-19 vaccinations are limited due to the recent approval of these vaccines following the pandemic (Dar-Odeh *et al*., 2022). The introduction of new mRNA-based and other new technologies in COVID-19 vaccine development for the first time requires further attention and continuous mentoring of LTSE (Kadali *et al*., 2021). Furthermore, a lot of studies have investigated the adverse reactions to COVID-19 vaccines mainly Pfizer-BioNTech, AstraZeneca, and Moderna (Kadali *et al*., 2021; Menni *et al*., 2021; Riad *et al*., 2021). However, few studies evaluated the adverse effects of Sinopharm vaccine (Hatmal *et al*., 2021; Saeed *et al*., 2021). This study provides an epidemiological report for COVID-19 vaccines LTSE in Jordan and provides an analysis of factors contributing to the occurrence of these LTSE. The mean duration between the first vaccine dose and the time of the study was 507.46 ±131.87 days with more than 90% of participants passed one year.

The associations between age, gender, obesity, and smoking with chronic diseases overall or with certain chronic diseases reported in this study are very well-known as reported previously (Zhu *et al*., 2014) and observed by similar studies in Jordan (Khader *et al*., 2008). COVID-19 infection frequency, severity, hospitalization, and death rate proved to increase with age, male gender, obesity, chronic diseases, smoking, and other risk factors (Liu *et al*., 2020b). However, in this study, participants above 60 years of age with a significantly higher

frequency of obesity and chronic diseases had significantly lower rates of COVID-19 infections and recurrence. Also, males had lower rates of infection and recurrence. Mostly, this is related to the significantly higher frequency of booster doses (3rd dose) vaccination among these groups, consistent with other studies (Diesel *et al*., 2021) and emphasizing the protective effect of the third dose (McMenamin *et al*., 2022).

Approximately, 58.5% of the research population reported at least one STSE which is comparable to another study in Jordan (46.3%) (Abu-Halaweh *et al*., 2021) and other countries (60%) (Alhazmi *et al*., 2021). The most frequent STSE was fatigue (37.1%) followed by myalgia (28.6%), fever (27.8%), pain and redness at the injection site (26%), and headache (22.9%), in contrast to other studies where the pain at the injection site was the most frequently reported adverse effect (Abu-Halaweh *et al*., 2021; Zahid, 2021). The highest frequency of STSE reported in the AstraZeneca group followed by Pfizer-BioNTech, then Sinopharm is consistent with the findings of other studies (Alhazmi *et al*., 2021; Alqassieh *et al*., 2021; Dawoud *et al*., 2022). The frequency of adverse effects was similar after the first 2 doses of Pfizer-BioNTech and Sinopharm in contrast to AstraZeneca, which was higher after the second dose of the vaccine. This is not consistent with other studies that reported a higher frequency of adverse effects after the first dose compared to the second dose (Zahid, 2021). The third dose's STSE was lowest compared to the first 2 doses for both Pfizer-BioNTech or Sinopharm which is best justified by the long interval between the 2nd and the third doses. This could be due to the decreased cumulative effect of doses and the difference in the type of the vaccine in many people compared to the first 2 doses.

There is a statistically significant association between age and STSE with the least reported adverse effect frequencies being lowest in the above 60 age group and highest in below 20 age group. Fatigue was the most frequent STSE for below 60 age group while pain at the injection site was the most frequent for above 60 age group which correlates with findings from another study outside Jordan (Green *et al*., 2022). Females have reported more STSE than males consistent with another study's findings (Saeed *et al*., 2021). There was a statistically significant relationship between previous COVID-19 infection and STSE which contradicts the finding from another study outside Jordan that reported no significant difference (Lai *et al*., 2022). In this study, no systemic life-threatening STSE was reported, and the overall rate of the adverse effects was within the familiar range of these vaccines.

Few studies were done on the LTSE of COVID-19 vaccines, but this study provides a detailed analysis of LTSE in Jordan. 100% of study participants reported at least one LTSE, in contrast to another study done in 2021 in Saudi Arabia and Jordan, only 16.1% of participants reported at least one LTSE (Dar-Odeh *et al*., 2022). This can be explained by the time difference among studies as this study was done during 2022/2023, after a longer period after vaccine administration. A lot of LTSE becomes evident after a latent period and people usually take a long time to note a difference in their baseline. The most frequent LTSE was fatigue followed by loss of concentration and mood changes, while the least reported adverse effects were jaundice and bloody urine consistent with another study finding (Dar-Odeh *et al*., 2022). The frequencies of adverse effects were comparable for the first 2 doses but lower after the third dose, most likely due to longer duration between the second and third doses, the same trend as that of STSE. Patients receiving Sinopharm reported more frequencies for most of the LTSE effects than Pfizer-BioNTech after the third dose.

5.2% of participants received a diagnosis for a new disease after vaccination, most commonly being joint diseases. As consistent with other study findings, there was no statistically significant difference between males and females in this concern. In contrast, others reported more frequent arthritis in females (Chen *et al*., 2022; Chen and Chen, 2023). The highest percent of the newly diagnosed diseases was in the Pfizer-BioNTech vaccine group and the least in the AstraZeneca group. 9.7% of participants reported increasing in previous diseases severity including most chronic diseases, especially hypertension, diabetes mellitus (DM), cardiac diseases, and thyroid diseases. Other studies reported that the vaccine increases blood pressure in previously hypertensive patients and leads to poorer glycemic control in patients with DM, especially who take insulin and oral hypoglycemic agents (Angeli *et al*., 2022; Heald *et al*., 2021).

A statistically significant relationship between the rate of LTSE and gender is found to be more frequent in men. Fatigue was more reported in the elderly, smokers, and individuals with chronic diseases. This might be because these groups have little reserve in their bodies, making them more sensitive to notice changes related to their health status. Smokers reported more anemia-related symptoms. Smokers need higher basal hemoglobin levels compared to non-smokers. Hence, any reduction in hemoglobin makes them feel anemic even if they have near normal hemoglobin levels, known to be sufficient for smokers (Nordenberg *et al*., 1990).

The aim of this study is to determine the LTSE of available COVID-19 vaccines in Jordan, specifically Pfizer-BioNTech, Sinopharm, and AstraZeneca, comparing the frequencies of LTSE between them, analyzing the factors that affect the adverse effects and noticing the difference between LTSE and STSE trends. A few studies were conducted in Jordan about COVID-19 vaccine adverse effects and people's hesitancy toward vaccines, but all investigated STSE. Studies that analyzed LTSE are few in the world. These studies can decrease the hesitancy of people toward vaccination as a lot of rumors confuse the general opinion against vaccination benefits (Aloweidi *et al*., 2021). The best method to report most of the COVID-19 vaccine adverse effects, especially the serious ones, is to establish a public surveillance web portal in each country and increase people's awareness toward using. A good example of that lies in the United States, where a reporting system for vaccine adverse effects at a governmental level was issued just after the launching of vaccine campaign (Gee *et al*., 2021). In Jordan, there is a governmental reporting system, but most people are not aware of it which limits its utility, thus the hesitancy among Jordanians is still present (MOH 2023b).

The main limitation of this study is that it is an observational cross-sectional study that depends mainly on the Google Forms platform administrated via various methods including but not limited to personal interviews, social media platforms, and patient encounters. Although

this enabled us to reach the largest number of patients from different categories of people which gave a good distribution of social characteristics of the participants, it limited the ability to define precisely the adverse effects in patient words. The subjectivity of many adverse effects and the severity of each adverse effect are other limitations of the study. Many adverse effects can be affected by external factors like socioeconomic factors that were greatly disrupted during the pandemic. Other factors include the mood of the patients, individual tolerability and patient perspective about vaccines affected greatly by common rumors regarding safety issues. The unawareness of people in Jordan of the national adverse effects reporting system, which makes it not an effective system, limits the knowledge about infrequent adverse effects that may be serious. So, we recommend increasing people's awareness about this reporting system and using it to note every minor possible adverse effect and follow up with the patient to know the nature of all adverse effects in terms of reversibility and progression to avoid such limitations in future studies.

5. Conclusions

In conclusion, the results of this study suggest that a considerable subset of COVID-19 vaccine recipients may experience LTSE. At least one LTSE was reported by all study participants. Fatigue, decreased concentration, and mood disturbances were the most reported LTSE among the study population (>30.0%). COVID-19 vaccine type has been identified as a key factor with Sinopharm vaccine-recipients having the highest frequency of reported LTSE while AstraZeneca vaccine recipients had a significantly higher frequency of most STSE. A dose-dependent effect of vaccines was associated with increased frequency of some STSE and LTSE. Furthermore, male gender, old age, smoking, chronic co-morbidities, and multiple COVID-19 infections contributed significantly to reported LTSE. Reported LTSE are vaccine type- and dose-dependent; however, a direct causal link is difficult to establish since other contributing factors have been identified. The nature of the reported LTSE is generally mild and its significant effects on quality of life are unlikely. Attention and follow-up of individuals at higher risk of developing LTSE are warranted. Further studies are needed, employing multidisciplinary teams of various medical professionals to investigate post-vaccination symptoms in different populations, and establish future interventions and policies.

6. Author Contributions

Conceptualization, A.A-S., M.A-K., and M.A-T.; methodology, A.M and R.D.; validation, A.A-S., A.Q and M.A-T., and M.M.A.; formal analysis, M.A-T.; data curation, A.A-S., M.A-T., A.M., R.D., A.Q., M.M.A., B.A-R., A.A-A., and M.A-K. writing—original draft preparation, A.M., R.D., B.A-R., A.A-A., and M.A-K; writing—review and editing, A.A-S., M.A-T., A.M., R.D., A.Q., M.M.A., B.A-R., A.A-A., and M.A-K.; supervision, M.A-T.; project ad-ministration, M.A-T.; funding acquisition, A.A-S. All authors have read and agreed to the published version of the manuscript .

7. Funding

This research was funded by the Deanship of Scientific Research, the Hashemite University, Zarqa, Jordan.

8. Institutional Review Board Statement

The study was approved by the institutional review board (IRB) at the Hashemite University (Reference No.22/4/2021/2022). Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data is available upon request.

Acknowledgments

We would like to thank Dr. Ola Soudah from the Department of Basic Medical Sciences, Faculty of Medicine, Yarmouk University, Irbid, Jordan for assistance with statistical analysis.

Conflict of Interests

The authors declare no conflict of interests.

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