Association of side effects of Covid 19 Vaccines with respect to gender.

Bushra Habib[1], Shamim Asim[2], Samreen Khan[3], Adeeba Salahuddin[4], Mahjabeen Saleem[5], Ahsan Ali Siddiqui[6]

[1]Basic Health Unit Sindh Government
[2]Department of Physiology Jinnah Sindh Medical University
[3]Department of Family Medicine, Indus Hospital Karachi
[4]Emergency Medicine Ziauddin Medical University
[5]Emergency Medicine Indus Hospital
[6]Family Medicine Ministry of Health Riyadh, KSA

ABSTRACT

Objective: Vaccination has been the sole effective treatment, from the time when the Coronavirus-19 was declared as a pandemic infection. Public's perception of the COVID-19 vaccine and the process of vaccination uptake is significantly impacted by its side effects. The purpose of this study was to compare the side effects experienced by men and women who received the COVID-19 vaccination.

Methodology: This was an observational cross-sectional multicenter study using a questionnaire to collect information from the participants. The study duration was about 6 months from july 2022 till Jan 2023 after obtaining approval. A total of 516 participants who received one of COVID-19 vaccines, such as Sinopharm, Sinovac, Astrazeneca, and Pfizer were included in the study. Demographic information about the participants', for instance, gender, age, comorbidities, vaccine type and dose, previous exposure to COVID-19 infection, and the occurrence of any systemic and local side effects after receiving the 1st and 2nd doses of vaccines were documented. The frequency of adverse effects was evaluated separately among males and females using the Chi-square test. An independent t-test was applied to assess the difference between means.

Results: Out of 516 participants,262(50.8%) were males and 256(49.6%) were females. Most of the male participants 118(45.1%) and female participants 95(37.1%) received Sinovac vaccine. Sinopharmvaccine was received by 60(22.9%) male participants and 63(24.6%) female participants. Pfizer was received by 64(24.4%) male participants and 58(22.7%) female participants, with a significant association observed between all vaccines and gender, (p=0.001). Following the 1stand 2nddoses of vaccines, the risk of side effects was higher in females. Pain, swelling, and a burning sensation at injection site were the most commonly observed side effects predominantly in females.

Conclusion: The study concluded that pain, swelling, burning sensation at the injection site, and fever were observed to be the most common side effects of the COVID-19 vaccines. Additionally, the most of the adverse effects associated with COVID-19 vaccinations were mild and well-tolerated. However, females were more likely to have these adverse effects than males.

Keywords: Adverse effects, gender disparities, pain, swelling, fever.

INTRODUCTION

The Coronavirus pandemic poses a serious risk to public health and has had a significant influence on a number of societal facets [1]. Millions of cases of disease and fatalities had been documented [2]. Coronavirus disease 2019 (COVID-19), in addition to having negative health effects, it has a significant economic impacts as well [3]. The need for safe and efficient vaccinations to defend vulnerable populations and return people's lives to their pre-disease states is urgent given the disease's alarming rate of spread and the excessive cost of relying entirely on non-pharmaceutical approaches [4,5]. Consequently, vaccinations are a safe and efficient method of lowering disease burdens globally [6]. It is commonly agreed that of all human activities, vaccination has had the greatest positive influence on world health [7]. The WHO deemed healthcare professionals the first group to receive the immunization since they are already at a high risk of illness [8].

People are immunized against the COVID-19 inflection by a number of safe and effective vaccinations [9]. However, due to the vaccines' speedy production, several concerns regarding their safety have arisen. [10] Following the introduction of COVID-19 vaccinations to general populations in several nations throughout the world, certain detrimental impacts were documented. [11-13] Vaccines, similar to all medicines, can have adverse effects. The majority of them are transitory and mild to moderate in severity [14]. According to studies, the COVID-19 vaccination might cause serious responses such deep vein thrombosis, transverse myelitis, and even anaphylaxis [15,16]. The Centers for Disease Control and Prevention (CDC) and other researches have documented adverse reactions to the COVID-19 vaccine, including local reactions like pain, inflammation, and redness around the injection site along with systemic reactions like arthritis, fatigue, backache, muscle aches, headache, shivers, pyrexia, and vomiting [17–20].

It is thought that the biological variations between men and women have a role in the gender-specific vaccination reactions. [21] The significant role of gender and sexuality has been emphasized during the COVID-19 pandemic [22].Despite having almost the same rate of infection, males had a nearly threefold greater chance of being admitted to critical care as well as a 40% higher death incidence from COVID-19 than females. The physiologic differences in

innate and adaptive immune responses between men and women can help to explain some of the reported differences [22]. This may be caused by the fact that immune responses differ between men and women, or it may be due to unique SARS-CoV-2 infectious properties that depend on the virus's ability to attach to the X-chromosome-encoded ACE2 receptor [23]. Numerous research were conducted in Arabian nations like Saudi Arabia and Jordan to identify adverse effects after receiving COVID-19 vaccinations according to the specific type of vaccine [24, 25].

Only two randomized clinical trials (RCTs) and a small number of observational studies have examined the gender disparity in the adverse effects of the COVID-19 vaccination, despite the fact that there have been numerous research on the effectiveness and safety of these vaccines. Regarding vaccination effectiveness, gender differences were not explained. [23]. Women, on the other hand, were far more likely than males to experience adverse effects. [22]. According to the findings from the study by Riad et al, females were more likely than males to have undesirable side effects following vaccination. [10].

Although there have been several research on the effectiveness and safety of COVID-19 vaccinations, to our knowledge, there have only been a small number that describe the gender discrepancy in the adverse effects of COVID-19 vaccines. Therefore, the purpose of this study was to examine the occurrence and severity of side effects following COVID-19 vaccination in males and females.

METHODOLOGY

This was an observational cross-sectional multicenter study using a questionnaire to collect information from the participants. The participants of the study were recruited using a convenience sampling approach. The protocol of the study was approved by the EthicalReview Committee.The study duration was about 6 months from July 2022 till Jan 2023 after obtaining approval. A total of 516 participants who received one of COVID-19 vaccines,such as Sinopharm, Sinovac, Astrazeneca,and Pfizer were included in the study. Failure to give the consent and incomplete proforma were included in the study . .

The participants' information was collected using a self-designedquestionnaire. Demographic information about the participants',for instance,gender, age, comorbidities, vaccine type and dose, previous exposure to COVID-19 infection, and the occurrence of any systemic and local adverse effects after receiving the 1st and 2nd doses of vaccines were documented. The satisfaction levels of participants were also documented.

Data was entered and analyzed by using SSPS version 20.0. By employing means, standard deviation and other descriptive statistics, different demographic parameters (sex, age, type of vaccine, number of doses, local and general side effects) were compared on gender basis. The frequency of adverse effects was evaluated separately among males and females using the Chi-square test. An independent t-test was applied to compare the association between means. A statistically significant p-value is considered less than 0.05.

RESULTS

A total of 516 participants after receiving COVID-19 vaccines were included in the study. Among them, 262(50.8%) were males and 256(49.6%) were females. The mean age of males was 42.7±14.0 years and the mean age of females was 39.04±14.6 years with a significant difference between them, (p=0.004). The mean weight of males was 67.2±14.4 kg and mean weight of females was 66.1±17.4 kg with an insignificant difference between them, (p=0.464).. Out of 516 participants, 56(21.4%) were hypertensive males and 58(22.7%) were hypertensive females, with an insignificant association between them, (p=0.725). Moreover, 62(23.7%) were diabetic males and 48(18.8%) were diabetic females, with an insignificant association between them, (p=0.172). The mean duration of hypertension was 5.50±5.28 years in males and 4.22±2.12 in females, with an insignificant association between them, (p=0.091). The mean duration of diabetes was 4.19±4.49 years in males and 3.69±2.48 in females, with an insignificant association between them, (p=0.475).. Concerning the type of injected vaccine, Sinopharm was received by 60(22.9%) male participants and 63(24.6%) female participants. Sinovac was received by 118(45.1%) male participants and 95(37.1%) female participants. Astrazeneca was received by 20(7.6%) male participants and 40(15.6%) female participants. Pfizer was received by 64(24.4%) male participants and 58(22.7%) female participants, with a

significant association observed between all vaccines and gender, (p=0.001). Approximately, 26(9.9%) male participants and 32(12.5%) female participants received the 1st and 2nd dose of vaccine whereas, 236 (90.1%) male participants and 224(87.5%) female participants received the 1st and 2nd dose along with a booster dose of vaccine, although there was an insignificant association observed among them, (p=0.316), as shown in Table I.

Following the 1stdose, the risk of side effects was higher in females. Pain was experienced by 106(40.5%) male and 132(51.6%) female participants, with a significant difference observed among them, (p=0.011). Swelling at the injection site occurred in most of the female participants 120(46.9%), and 92(35.1%) in male participants, with a significant difference (p=0.006). Fever was reported in 178(69.5%) female and 116(44.3%) male participants, with significant association observed between genders, (p<0.001). Furthermore, burning at the injection site was felt by 148(57.8%) female and 92(35.1%) male participants with a significant difference between gender, (p<0.001). Moreover, nausea, rashes, anxiety, fatigue, , swelling of the glands, and chest pain were significantly associated with both genders (p<0.001). On the other hand, an insignificant association observed between redness at the injection site, lymphadenopathy, headache, flu, muscle pain, joint pain, chills, cough, and diarrhea and both genders (p>0.001), as shown in Table II.

The distribution of side effects after the 2nddose of COVID-19 vaccine among the participants revealed that most commonly observed side effect was burning at the injection site,which was felt by 132(51.6%) female and 80(30.5%) male participants with a significant difference between genders (p<0.001). pain experienced in 90(34.4%) male and 124(48.4%) female participants, with a significant difference observed among them (p=0.001). Fever was reported in 110(43.0%) female and 96(36.6%) male participants, with an insignificant association observed between genders (p=0.141). Furthermore, rashes developed in 100(39.1%) female and 76(29.0%) male participants, with a significant difference between genders (p=0.016). Moreover, lymphadenopathy, headache, nausea, joint pain, chills, swelling of glands, diarrhea, and chest pain were significantly associated with both genders (p<0.001). On the other hand, an insignificant association was observed between swelling and redness at injection site, flu, anxiety, fatigue, , shortness of breath, cough, and sore throat in both genders (p>0.001), as shown in Table III.

The majority of the male 142(54.2%) and female 137(53.5%) participants were satisfied with their vaccination. While, only 8(3.1%) males and 4(1.6%) females were dissatisfied, there was an insignificant association observed with respect to genders (p=0.076), as shown in Table IV.

Table I:The participants' basic demographic characteristics (n=516).

Variable		**Male Mean±SD n(%)**	**Female Mean±SD n(%)**	**p-value**
Age (years)		42.7±14.0	39.04±14.6	0.004
Weight (kg)		67.2±14.4	66.1±17.4	0.464
Hypertension Duration (years)		5.50±5.28	4.22±2.12	0.091
Diabetes Mellitus Duration (years)		4.19±4.49	3.69±2.48	0.475
Hypertension	**Yes**	56(21.4%)	58(22.7%)	0.725
	No	206(78.6%)	198(77.3%)	
Diabetes Mellitus	**Yes**	62(23.7%)	48(18.8%)	0.172
	No	200(76.3%)	208(81.3%)	
Type of vaccine	**Sinopharm**	60(22.9%)	63(24.6%)	0.001
	Sinovac	118(45.1%)	95(37.1%)	
	Astrazeneca	20(7.6%)	40(15.6%)	
	Pfizer	64(24.4%)	58(22.7%)	
Vaccination status	**Vaccinated with 1st and 2nd dose**	26(9.9%)	32(12.5%)	0.316
	Vaccinated with Booster Dose	236 (90.1%)	224(87.5%)	

Table II: The distribution of side effects of COVID-19 vaccine after 1st dose of COVID-19 vaccine among the participants.

Variable	Male		Female		p-value
	Yes n(%)	No n(%)	Yes n(%)	No n(%)	
Pain at injection site	106(40.5%)	156(59.5%)	132(51.6%)	124(48.4%)	0.011
Swelling at injection site	92(35.1%)	170(64.9%)	120(46.9%)	136(53.1%)	0.006
Redness at injection site	42(16.0%)	220(84.0%)	56(21.9%)	200(78.1%)	0.090
Lymphadenopathy	58(22.1%)	204(77.9%)	64(25.0%)	192(75.0%)	0.443
Fever (temperature >37.8 ˚C)	116(44.3%)	146(55.7%)	178(69.5%)	78(30.5%)	<0.001
Headache	58(22.1%)	204(77.9%)	67(26.2%)	189(73.8%)	0.283
Nausea	20(7.6%)	242(92.4%)	40(15.6%)	216(84.4%)	0.004
Rashes	62(23.7%)	200(76.3%)	92(35.9%)	164(64.1%)	0.002
Burning at injection site	92(35.1%)	170(64.9%)	148(57.8%)	108(42.2%)	<0.001
Flu	42(16.0%)	220(84.0%)	40(15.6%)	216(84.4%)	0.899
Anxiety	48(18.3%)	214(81.7%)	84(32.8%)	172(67.2%)	<0.001
Muscle pain (Myalgia)	72(27.5%)	190(72.5%)	83(32.4%)	173(67.6%)	0.220
Fatigue	62(23.7%)	200(76.3%)	87(34.0%)	169(66.0%)	0.009
Joint pain	82(31.3%)	180(68.7%)	96(37.5%)	160(62.5%)	0.137
Anaphylaxis	56(21.4%)	206(78.6%)	92(35.9%)	164(64.1%)	<0.001
Chills	78(29.8%)	184(70.2%)	96(37.5%)	160(62.5%)	0.063
Cough	46(17.6%)	216(82.4%)	60(23.4%)	196(76.6%)	0.097
Swelling of glands	48(18.3%)	214(81.7%)	68(26.6%)	188(73.4%)	0.024
Sore throat	70(26.7%)	192(73.3%)	88(34.4%)	168(65.6%)	0.058
Shortness of breath	54(20.6%)	208(79.4%)	71(27.7%)	185(72.3%)	0.058

Diarrhea	42(16.0%)	220(84.0%)	52(20.3%)	204(79.7%)	0.206
Chest Pain	38(14.5%)	224(85.5%)	76(29.7%)	180(70.3%)	<0.001

Table III: The distribution of side effects after 2nddose of COVID-19 vaccine among the participants.

Variable	Male		Female		p-value
	Yes n(%)	No n(%)	Yes n(%)	No n(%)	
Pain at the site of injection	90(34.4%)	172(65.6%)	124(48.4%)	132(51.6%)	0.001
Swelling at the site of injection	90(34.4%)	172(65.6%)	99(38.7%)	157(61.3%)	0.307
Redness at the site of injection	24(9.2%)	238(90.8%)	32(12.5%)	224(87.5%)	0.221
Lymphadenopathy	50(19.1%)	212(80.9%)	100(39.1%)	156(60.9%)	<0.001
Fever (temperature >37.8 ˚C)	96(36.6%)	166(63.4%)	110(43.0%)	146(57.0%)	0.141
Headache	56(21.4%)	206(78.6%)	88(34.4%)	168(65.6%)	0.001
Nausea	14(5.3%)	248(94.7%)	4(1.6%)	252(98.4%)	0.019
Rashes	76(29.0%)	186(71.0%)	100(39.1%)	156(60.9%)	0.016
Burning at injection site	80(30.5%)	182(69.5%)	132(51.6%)	124(48.4%)	<0.001
Flu	40(15.3%)	222(84.7%)	48(18.8%)	208(81.3%)	0.291
Anxiety	56(21.4%)	206(78.6%)	72(28.1%)	184(71.9%)	0.075
Muscle pain (Myalgia)	74(28.2%)	188(71.8%)	108(42.2%)	148(57.8%)	0.001
Fatigue	56(21.4%)	206(78.6%)	68(26.6%)	188(73.4%)	0.166
Joint pain	68(26.0%)	194(74.0%)	96(37.5%)	160(62.5%)	0.005
Anaphylaxis	52(19.8%)	210(80.2%)	56(21.9%)	200(78.1%)	0.570
Chills	68(26.0%)	194(74.0%)	96(37.5%)	160(62.5%)	0.005
Cough	32(12.2%)	230(87.8%)	24(9.4%)	232(90.6%)	0.298
Swelling of glands	66(25.2%)	196(74.8%)	112(43.8%)	144(56.3%)	<0.001
Sore throat	36(13.7%)	226(86.3%)	48(18.8%)	208(81.3%)	0.122
Shortness of breath	70(26.7%)	192(73.3%)	88(34.4%)	168(65.6%)	0.058

Diarrhea	38(14.5%)	224(85.5%)	60(23.4%)	196(76.6%)	0.009
Chest Pain	52(19.8%)	210(80.2%)	80(31.3%)	176(68.8%)	0.003

Table IV: Association of serious adverse effects with respect to gender.

Variable		**Male n(%)**	**Female n(%)**	**p-value**
Overall subject level of Satisfaction for vaccine	**Very Satisfied**	68(26.0%)	52(20.3%)	0.076
	Satisfied	142(54.2%)	137(53.5%)	
	Neutral	44(16.8%)	63(24.6%)	
	Dissatisfied	8(3.1%)	4(1.6%)	

DISCUSSION

The pandemic COVID-19 infection poses a serious risk to public health, and immunizations are a reliable and efficient strategy to lower disease burdens globally [26]. This study demonstrated the gender differences in adverse effects following the COVID-19 vaccine among the population in Pakistan.

In one of the research done in Iraq, 843 health care workers (HCWs) from various cities were involved. Females represented the majority of responders (664). Approximately 65% of men and 77% of women reported adverse consequences. Women reported experiencing acute pain quite frequently. Female respondents also reported more dermatological effects, such as edema, burning, and skin rashes. Additionally, females experienced milder to moderate nausea and greater incidences of moderate or severe systemic side effects than did males. This could be connected to their hormonal and psychological influences [27]. These findings were inconsistent with the present study and showed that the majority of the participants were male 262(50.8%). Regarding side effects, most commonly reported side effect after the first dose of vaccination was fever 178(69.5%) followed by pain 132(51.6%) in female participants. Additionally, burning

sensation 132(51.6%) followed by pain 124(48.4%) following the second dose, was also most commonly reported in females. Females were most commonly reported side effects that can be elucidated by the fact hormonal and psychological factors related to females.

Similar findings were made in another study, which found that overall side effects were mild, tolerable, and self-limiting in both sexes, however women reported more side effects than men did [27]. These findings were in accordance with the present study and showed that females experienced more side effects as compared to males; however, serious adverse events were more common in males than females following the 1st and 2nd doses of vaccines.

Likewise, a cross-sectional research among the general population in Malaysia found that females similarly experienced more undesirable effects than males [28]. Women were also more likely to develop both local and systemic side effects in a different study conducted in Germany by Hoffman et al. to assess the probability of local and systemic adverse effects following immunization with COVID-19 vaccines. Complications from vaccinations or allergic responses, however, were not found. These results concurred with those of the Centers for Disease Control and Prevention (CDC) publications [29]. The present study was consistent with the above mentioned research and revealed that overall, females experienced more side effects than males.

A research conducted in Saudi Arabia to investigate post-vaccination adverse effects among the general population. They discovered that men suffer higher adverse effects than women [12]. In contrast to that study, the present study reported that females experienced more adverse effects compared to males.

The most frequent side effect was pain at the injection site, and for the majority of respondents, this pain was not severe enough to need treatment. Females reported experiencing severe pain more often than males did. Although it is unclear what exactly causes these gender disparities [27]. There are several biological and psychological elements that seem to be significant contributors. Less than half of the participants in an observational research conducted in the UK to report adverse effects following vaccination with Pfizer and AstraZeneca vaccines among the general population reported having pain at the injection site, and it is more prevalent in women

[30]. According to Hoffman et al research, 78% of men and 72% of women in their study reported having no pain [29]. Numerous studies suggest that sex hormones affect pain sensitivity, whereas some hypotheses suggest that endogenous opioids and inheritance both play key roles in these variances. Psychosocial mechanisms, such as stress exposure and the capacity to deal with pain, might potentially account for the gender difference in pain threshold in addition to conventional sex roles that may contribute to inequalities in pain expression [31]. In terms of systemic symptoms like headache, fatigue, muscle aches, chills, and fever, women had moderate and severe side effects at much higher rates than males. A research by Menni et al. found that headaches were more prevalent in women [30]. Headaches, chills, and pyrexia were also more prevalent in women in a research conducted in Germany to investigate the prevalence of side effects following immunization with one of the COVID-19 vaccines among HCWs [32]. The results of the present study were corroborated with all the above research and indicated that pain at the injection site was more commonly reported in females than males following vaccination. Besides pain, burning sensations and swelling were also more commonly observed in females than in males. In the aspect of systemic symptoms such as headache, tiredness, myalgia, chills, fever, anxiety, shortness of breath and chest pain were significantly greater in women.

In terms of the dermatological symptoms, female individuals were more likely to experience edema, rashes, and redness [27]. Although there was no statistically significant difference between males and females in the German trial, females also had higher edema and redness [29]. According to a CDC research, while they are uncommon, 90% of allergy reactions were observed in females [33]. The present study findings were similar to the above mentioned studies, showing dermatological side effects were more common in females such as swelling, skin rash, and redness, although the difference between them and males was significant with respect to swelling and rashes following the 1st dose of vaccination, ($p<0.001$).

In a 2019 research to record vaccine side effects to the CDC from 1990 to 2016, women reported 80% of adults' severe allergic reactions (anaphylaxis) [34]. These findings were partially consistent with the present study and revealed that the anaphylaxis was reported more in females

as compared to males and significantly associated between both genders following 1st dose ($p<0.001$) while insignificant after 2nd dose, ($p=0.570$).

Despite the large sample size, the research had numerous drawbacks, including a lack of information about the participant's medical history, including any medication or pulmonary problem history. Researchers mainly looked at the short-term negative effects of immunizations; longer-term study in the general public is required. It is also advised to do a more extensive research that includes all certified vaccinations.

CONCLUSION

The study concluded thatpain, swelling, burning sensation at the injection site, and fever were observed to be the most common side effects of the COVID-19 vaccines. Additionally, the most of the adverse effects associated with COVID-19 vaccinations were mild and well-tolerated. However, females were more likely to have these adverse effects than males.Consequently, theseresults suggest that different vaccination dosages for men and women should be investigated.

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