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Sars-cov-2 vaccination and associated side effects among Saudi general population

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ABSTRACT

Background: Unless vaccines are approved and widely used, there will be over 400 million cases of coronavirus illness (COVID-19) in 2019. This is less than two years after the World Health Organization called it a pandemic. Vaccines, on the other hand, may have individual-level side effects that warrant additional research. *Objective:* The study's aim was to identify the adverse effects reported by the Saudi population in relation to the COVID-19 vaccines. *Methodology:* A cross-sectional observational study was held in Saudi Arabia between March 1, 2022, and April 15, 2022. *Results:* The study comprised 3463 adults ranging in age from 18 to 94 years old, with an average age of 33.4 years. The type of vaccine had a statistically significant association with fever, joint pain, lower limb edema, nausea, abdominal discomfort, sweating, distal limb tingling, vertigo), chest pain, sleepiness or drowsiness, and arrhythmia or tachycardia. *Conclusion:* The lower incidence of fever, joint discomfort, lower limb edema, nausea, abdominal pain, sweating, distal limb tingling, vertigo, drowsiness, and tachycardia were associated with Pfizer vaccine. Lower incidences of chest pain were associated with AstraZeneca vaccine.

Keywords: SARS-CoV-2, Vaccination, Side Effects, Saudi Population

1. INTRODUCTION

By the end of January 2022, the coronavirus disease 2019 (COVID-19) would have surpassed 400 million cases, less than two years after the World Health Organization labelled it a pandemic (Dong et al., 2020). The most prevalent sign of severe COVID-19 is the development of interstitial pneumonia, which can range in severity from asymptomatic to moderate and self-limiting to severe illness with the acute respiratory syndrome (SARS-CoV-2) necessitating ICU hospitalization and mechanical ventilation (Struyf et al., 2020; Viner et al., 2020).

New variations of the virus that causes COVID-19 are emerging as the pandemic progresses, making the virus easier to spread (Dooling et al., 2021), making it vital to deploy public health techniques to limit the virus, minimize disease, and finally stop the pandemic. As vaccines have been approved for use and are being distributed to the highest-priority individuals, including healthcare providers (Dooling et al., 2021), it is critical that accurate and timely

information be provided to encourage these individuals to get vaccinated when vaccines become available. With vaccine supplies and countrywide distribution continuing to be inconsistent, the availability of COVID-19 vaccinations, especially for those who need them most, remains questionable. The COVID-19 pandemic was characterized by uncertainty since many signals concerning preventative care and what to do if infected with the virus were unclear. Aside from ambiguous messaging, there has been a great deal of disinformation concerning the virus and, more recently, vaccinations and their efficacy (Chou et al., 2021). As a result, people's trust in COVID-19 vaccinations and the protection they can give has eroded.

Vaccination is one of the most cost-effective, safe, and reliable strategies for decreasing illness, mortality, disability, and inequity globally, according to the World Health Organization (Andre et al., 2008). Vaccines, on the other hand, are frequently misunderstood, and the concept of vaccination can be daunting to certain people, which are sometimes referred to as "vaccine hesitancy (Kulkarni & Khurana, 2022)." Vaccine hesitancy, according to the SAGE Working Group on Vaccine Hesitancy, is defined as a delay in accepting or refusing immunization notwithstanding the availability of vaccination services (MacDonald et al., 2015). Vaccine reluctance is a spectrum that ranges from fully intending to be vaccinated to being utterly opposed to immunization (Bedford et al., 2018). This means that people might be more or less "hesitant" about vaccination and consequently more or less supportive of it. The phrase “decisional conflict”, which represents the paradox of living in an unsure or indeterminate condition and is extensively used to study vaccination behaviour, can help to explain vaccine hesitation (Beatty et al., 2021; Bedford et al., 2018; Goldberg et al., 2021).

Study aim

The study aims to identify the untoward effects reported to be experienced in association with COVID-19 vaccines by the Saudi public.

2. METHODOLOGY

Study design

The study adopted a cross-sectional observational study design.

Study setting

The study took place in Saudi Arabia.

Study duration

The study was conducted from March 1, 2022, to April 15, 2022.

Study participants

Inclusion criteria

Saudi adults who have received a COVID-19 vaccination were included in this study (one, two, or three doses). The last shot, whether it was the first or second, should have been given no more than three months before the questionnaire was filled out.

Exclusion criteria

Individuals who were vaccinated for longer than three months were excluded from the study. Participation in this study was not compensated financially or by any other incentives.

Sample size

We utilized a nonprobability sampling technique (snowball sampling), where the subjects that were preliminarily recruited for participation were recruited by future subjects from colleagues and acquaintances from different societies and geographical locations in the KSA. The study collected 3463 complete responses that were included in the study.

Data collection

Data was collected using a modified self-administered adapted form from a similar study that was conducted in Jordan (Hatmal et al., 2021).

Processing and analysis of data

The Statistical Package for Social Sciences (SPSS) version 26 was used to analyze quantitative data. Data from questionnaires was coded before entry and checked before analysis. For the descriptive analysis, the mean and standard deviation were used to describe continuous variables. On the other hand, for categorical variables, tables of description, frequency, and percentage were used. We used the chi-square test for inferential analysis.

Ethical Considerations

Before the study's implementation began, approval from the relevant Institutional Review Board (IRB) was obtained. Moreover, since the study did not include any patient personal information, the consent form was included in the data collection form to be obtained from the respondents. The collected data was always kept confidential. The actual names and addresses of the participants will not be disclosed.

3. RESULTS

The study included 3463 adults whose average age was 33.4 years, as the age ranged from 18 to 94 years. Females comprised 68% of participants. Three-fourths (73.7%) of participants had an undergraduate degree, and the majority (90%) resided in an urban region. Our study included participants from all geographical regions in Saudi Arabia, with the most prominent contribution from the southern region (35.4%). Only 16.7% of participants were working in the healthcare system (Table 1). Table 2 shows the vaccination and health-related data among participants. The majority of participants did not report having any food or drug allergies (17.5%) and had no COVID-19 infection prior to vaccination (74.3%).

Table 2 shows the vaccination and health-related data among participants. The majority of participants did not report having any food or drug allergies (17.5%) and had no COVID-19 infection prior to vaccination (74.3%). Of all, diabetes was reported by 6% of the sample, followed by obesity (5.1%), hypertension (4.7%), bronchial asthma (4.7%), thyroid dysfunction (4.1%), and arthritis (2.9%). Governmental publications and the media were the sources of knowledge on COVID-19 vaccines among 55% of participants. After vaccination, 28.3% of participants reported having a COVID-19 infection. Over half (56.5%) did not think that the vaccines were safe eventually, and 44.1% did not feel safe after receiving the vaccine dose. Participants reported having mild (38%), moderate (31.1%), and severe (31.1%) side effects after the last vaccine dose.

Table 1 Sociodemographic characters of participants (n=3463).

Parameter		Frequency (%)
Age, y (Mean±SD [Min-Max])	33.4±11.1 (18-94)	
Sex	Female	2355 (68%)
	Male	1108 (32%)
Educational level	Secondary education or less	523 (15.1%)
	Undergraduate degree	2550 (73.7%)
	Postgraduate degree	390 (11.3%)
Occupation in healthcare facilities	No	2885 (83.3%)
	Yes	578 (16.7%)
Residency type	Rural	346 (10%)
	Urban	3116 (90%)
Region	Southern region	1226 (35.4%)
	Eastern region	498 (14.4%)
	Northern region	295 (8.5%)
	Western region	664 (19.2%)
	Central region	781 (22.6%)

Table 2 Vaccination and health-related data among participants (n=3463).

Parameter		Frequency (%)
Food or drug allergy	No	2856 (82.5%)
	Yes	607 (17.5%)
Chronic diseases	None	2596 (75%)

	Bronchial asthma	162 (4.7%)
	Cardiovascular diseases	46 (1.3%)
	Autoimmune diseases	29 (0.8%)
	Hypertension	164 (4.7%)
	Thyroid dysfunction	141 (4.1%)
	Cancer	10 (0.3%)
	Obesity	177 (5.1%)
	Arthritis	99 (2.9%)
	Diabetes	208 (6%)
	Osteoporosis	38 (1.1%)
	Others	99 (2.9%)
COVID-19 Infection prior to vaccination	No	2571 (74.3%)
	Yes	892 (25.7%)
COVID-19 Vaccines source of knowledge	Friends and family	162 (4.7%)
	Governmental media	1904 (55%)
	Medical and scientific websites	430 (12.4%)
	Social media	833 (24%)
	I do not have knowledge	135 (3.9%)
Did you feel worried before receiving the vaccine?	No	1536 (44.3%)
	Yes	1927 (55.7%)
Number of doses received	Three doses	2246 (64.9%)
	One dose	29 (0.8%)
	Two doses	1188 (34.3%)
Time of the last dose	Four months ago, or more	1813 (52.4%)
	Three months ago,	838 (24.2%)
	Last month	348 (10%)
	Two months ago,	464 (13.4%)
COVID-19 Infection after vaccination	No	2484 (71.7%)
	Yes	979 (28.3%)
Do you think that COVID-19 vaccines are safe on the longterm?	No	1956 (56.5%)
	Yes	1507 (43.5%)
Do you feel safe after receiving the vaccine?	No	1526 (44.1%)
	Yes	1937 (55.9%)
Do you think that social distancing and safety measuresare still necessary after vaccination?	No	1311 (37.9%)
	Yes	2151 (62.1%)
Did you check your vital signs more after the vaccination?	No	2339 (67.6%)
	Yes	1123 (32.4%)
Do you recommend COVID-19 vaccines for others?	No	1055 (30.5%)
	Yes	2408 (69.5%)
Type of last vaccine you received	Pfizer-BioNTech	2579 (74.5%)
	Oxford, AstraZeneca	341 (9.8%)
	Moderna	544 (15.7%)
Did you have side effects after the last vaccination?	No side effects	447 (12.9%)
	Yes, mild	1317 (38%)
	Yes, severe	622 (17.9%)
	Yes, moderate	1078 (31.1%)

Table 3 shows the prevalence of the self-reported side effects experienced after the last COVID-19 vaccine dose. Fatigue and tiredness (81.3%), injection site swelling (80.6%), headache (64.3%), fever (60.8%), sleepiness or drowsiness (58%), nausea (24.8%), vomiting (7.5%), gum bleeding (5.8%), nose bleeding (4.6%), thrombocytopenia (2.5%), and being diagnosed with thrombosis (2.2%) were all reported side effects. Table 4 show the distribution of the experienced side effects. The most reported side effect was fatigue (81.3%). It was mostly encountered following a dose of the AstraZeneca vaccine (86%); however, there was no significant association with the type of vaccine (p=0.074). There was a significant association between the type of vaccine and experience of fever (p = 0.001), joint pain (p = 0.005), lower limb edema (p=0.011), nausea (p=0.003), abdominal pain (p=0.020), sweating (p=0.047), distal limb tingling (p=0.000), vertigo (p=0.007), chest pain (p=0.000), sleepiness or drowsiness (p=0.021), and arrhythmia or tachycardia (p=0.003).

Table 3 Prevalence of the self-reported side effects experienced after the last COVID-19 vaccine dose (n=3463).

Side effect	Yes	No
Fatigue and tiredness	2814 (81.3%)	648 (18.7%)
Lower sleep quality	1610 (46.5%)	1853 (53.5%)
Fever	2104 (60.8%)	1359 (39.2%)
Headache	2227 (64.3%)	1235 (35.7%)
Cloudy vision	783 (22.6%)	2679 (77.4%)
Injection site swelling	2790 (80.6%)	673 (19.4%)
Joint pain	1969 (56.9%)	1494 (43.1%)
Lower limb edema	405 (11.7%)	3058 (88.3%)
Myalgia	1828 (52.8%)	1634 (47.2%)
Nausea	859 (24.8%)	2603 (75.2%)
Abdominal pain	620 (17.9%)	2843 (82.1%)
Diarrhea	479 (13.8%)	2983 (86.2%)
Vomiting	261 (7.5%)	3202 (92.5%)
Bruising	458 (13.2%)	3004 (86.8%)
Gum bleeding	202 (5.8%)	3261 (94.2%)
Nose bleeding	160 (4.6%)	3303 (95.4%)
Chills	1133 (32.7%)	2330 (67.3%)
Itching	588 (17%)	2875 (83%)
Sweating	848 (24.5%)	2615 (75.5%)
Distal limb tingling	969 (28%)	2493 (72%)
Vertigo	1076 (31.1%)	2387 (68.9%)
Nasal congestion	770 (22.2%)	2693 (77.8%)
Runny nose	751 (21.7%)	2712 (78.3%)
Difficulty breathing	842 (24.3%)	2621 (75.7%)
Chest pain	848 (24.5%)	2615 (75.5%)
Sleepiness or drowsiness	2007 (58%)	1456 (42%)
Arrhythmia or tachycardia	935 (27%)	2527 (73%)
Blood pressure changes	548 (15.8%)	2915 (84.2%)
Throat pain or dryness	1036 (29.9%)	2427 (70.1%)
Cough	641 (18.5%)	2822 (81.5%)
Diagnosed with thrombosis	76 (2.2%)	3386 (97.8%)
Thrombocytopenia	86 (2.5%)	3377 (97.5%)

Table 4 Distribution of the self-reported side effects across each type of COVID-19 vaccine (n=3463).

Side effect	Pfizer-BioNTech		Oxford, AstraZeneca		Moderna		P-value
	No	Yes	No	Yes	No	Yes	
Fatigue and tiredness	513 (19.9%)	2066 (80.1%)	48 (14%)	293 (86%)	88 (16.1%)	456 (83.9%)	0.074
Lower sleep quality	1418 (55%)	1161 (45%)	173 (50.8%)	168 (49.2%)	263 (48.3%)	282 (51.7%)	0.088
Fever	1076 (41.7%)	1503 (58.3%)	113 (33%)	228 (67%)	171 (31.5%)	373 (68.5%)	0.001
Headache	949 (36.8%)	1631 (63.2%)	109 (31.8%)	232 (68.2%)	179 (32.9%)	365 (67.1%)	0.242
Cloudy vision	2026 (78.6%)	553 (21.4%)	247 (72.6%)	94 (27.4%)	407 (74.8%)	137 (25.2%)	0.108
Injection site swelling	515 (20%)	2064 (80%)	73 (21.2%)	268 (78.8%)	86 (15.7%)	458 (84.3%)	0.210
Joint pain	1165 (45.2%)	1414 (54.8%)	139 (40.8%)	202 (59.2%)	190 (35%)	354 (65%)	0.005
Lower limb edema	2311 (89.6%)	268 (10.4%)	291 (85.5%)	50 (14.5%)	456 (83.9%)	88 (16.1%)	0.011
Myalgia	1234 (47.8%)	1346 (52.2%)	156 (45.8%)	185 (54.2%)	246 (45.1%)	299 (54.9%)	0.652
Nausea	1992 (77.2%)	588 (22.8%)	238 (69.8%)	103 (30.2%)	375 (68.9%)	170 (31.1%)	0.003
Abdominal pain	2151 (83.4%)	428 (16.6%)	257 (75.4%)	84 (24.6%)	436 (80.1%)	109 (19.9%)	0.020
Diarrhea	2229 (86.4%)	350 (13.6%)	299 (87.7%)	42 (12.3%)	456 (83.9%)	88 (16.1%)	0.436
Vomiting	2406 (93.3%)	173 (6.7%)	303 (88.8%)	38 (11.2%)	494 (90.9%)	50 (9.1%)	0.057
Bruising	2241 (86.9%)	339 (13.1%)	291 (85.5%)	50 (14.5%)	474 (87.1%)	71 (12.9%)	0.862
Gum bleeding	2444 (94.8%)	135 (5.2%)	312 (91.6%)	29 (8.4%)	506 (93%)	38 (7%)	0.156
Nose bleeding	2459 (95.4%)	120 (4.6%)	325 (95.5%)	16 (4.5%)	519 (95.5%)	25 (4.5%)	0.993
Chills	1754 (68%)	825 (32%)	240 (70.4%)	101 (29.6%)	337 (61.9%)	208 (38.1%)	0.086
Itching	2151 (83.4%)	428 (16.6%)	285 (83.8%)	56 (16.2%)	439 (80.8%)	105 (19.2%)	0.533
Sweating	1980 (76.8%)	599 (23.2%)	234 (68.7%)	107 (31.3%)	401 (73.8%)	143 (26.2%)	0.047
Distal limb tingling	1921 (74.5%)	658 (25.5%)	209 (61.5%)	132 (38.5%)	363 (66.8%)	181 (33.2%)	0.000
Vertigo	1826 (70.8%)	753 (29.2%)	227 (66.5%)	114 (33.5%)	335 (61.5%)	209 (38.5%)	0.007
Nasal congestion	2033 (78.9%)	546 (21.1%)	263 (77.1%)	78 (22.9%)	398 (73.1%)	147 (26.9%)	0.100
Runny nose	2020 (78.3%)	559 (21.7%)	280 (82.1%)	61 (17.9%)	413 (75.9%)	132 (24.1%)	0.282
Difficulty breathing	1978 (76.7%)	601 (23.3%)	255 (74.9%)	86 (25.1%)	388 (71.3%)	156 (28.7%)	0.150
Chest pain	1984 (76.9%)	595 (23.1%)	274 (80.4%)	67 (19.6%)	358 (65.7%)	187 (34.3%)	0.000
Sleepiness or drowsiness	1121 (43.5%)	1458 (56.5%)	147 (43%)	194 (57%)	189 (34.6%)	356 (65.4%)	0.021
Arrhythmia or tachycardia	1933 (74.9%)	646 (25.1%)	240 (70.4%)	101 (29.6%)	356 (65.4%)	189 (34.6%)	0.003
Blood pressure changes	2174 (84.3%)	405 (15.7%)	297 (87.2%)	44 (12.8%)	445 (81.8%)	99 (18.2%)	0.301
Throat pain or dryness	1832 (71%)	747 (29%)	246 (72.1%)	95 (27.9%)	350 (64.3%)	194 (35.7%)	0.066
Cough	2127 (82.5%)	453 (17.5%)	280 (82.1%)	61 (17.9%)	417 (76.6%)	128 (23.4%)	0.064
Diagnosed with thrombosis	2527 (98%)	52 (2%)	329 (96.6%)	12 (3.4%)	531 (97.6%)	14 (2.4%)	0.480
Thrombocytopenia	2518 (97.6%)	61 (2.4%)	327 (96.1%)	14 (3.9%)	532 (97.9%)	12 (2.1%)	0.411

4. DISCUSSION

Many governments and healthcare systems throughout the globe have faced unjustified challenges in carrying out their immunization campaigns due to widespread misinformation and misunderstandings about vaccinations. Recent reports of "vaccine-induced COVID-19 mimicry" syndromes causing adverse outcomes, such as thromboembolic events/blood clots, are attributed to the Oxford-AstraZeneca and Johnson & Johnson vaccines. Due to a rise in vaccine-related adverse effects in their nations, several European countries have even stopped utilizing the vaccines (Dotan and Shoenfeld, 2021). Our study aimed to identify the untoward effects reported to be experienced in association with COVID-19 vaccines by the Saudi public. The study included 3463 adults whose ages ranged from 18 to 94 years. Nearly three-fourths of respondents received the Pfizer-BioNTech vaccine for their last dose (74.5%).

Fatigue was the most frequently reported adverse effect (81.3%). It was most often seen after an AstraZeneca vaccination dosage (86%), although there was no significant connection with vaccine type (p=0.074). Fatigue was reported in several studies after vaccination with Pfizer or AstraZeneca vaccines, which supports our results (Kadali et al., 2021; Polack et al., 2020; Riad et al., 2021;

Marglani et al., 2021). In a study from Jordan (Omeish et al., 2022), however, a larger percentage of individuals who received Sinopharm vaccination complained of exhaustion than in the randomized controlled experiment (Xia et al., 2021). This was also supported by recent evaluation of 87 articles, including safety data from 19 COVID-19 vaccination clinical trials and post-authorization studies (Wu et al., 2021).

Our study found that 2.2% self-reported having been diagnosed with thrombosis following COVID-19 vaccination, where the highest prevalence of thrombosis was reported from those receiving the AstraZeneca vaccine (3.4%). In the United Kingdom, 309 persons out of 33 million who got the AstraZeneca vaccination had blood clots, with 56 of them dying. Similarly, in Europe, out of 16 million individuals, 142 persons had blood clots. The Saudi Food and Drug Administration recognized 34 occurrences of blood clots or thrombosis in persons who received the Oxford-Astra Zeneca vaccine, as well as low blood platelet counts. These unpleasant responses and terrible vaccine-related adverse events have instilled anxiety in the public's mind about vaccinations.

Serious side events, such as anaphylaxis or allergy, were uncommon in the digital cohort of 19586 patients who reported getting COVID-19 vaccination, according to Beatty et al., (2021). Adverse reactions were more likely after the full vaccination dosage, the mRNA-1273 vaccine, and in individuals, who were younger, female, had previously contracted COVID-19, were Asian, had been pregnant at the time of the study, and used marijuana. The lower likelihood of reporting unfavourable symptoms related to older age, Black or African American race, higher subjective social status, asthma, and anaemia (Beatty et al., 2021). The type of vaccine had a significant relationship with joint pain ($p=0.005$), lower limb edema ($p = 0.011$), nausea ($p = 0.003$), abdominal pain ($p = 0.020$), sweating ($p = 0.047$), distal limb tingling ($p = 0.000$), vertigo ($p = 0.007$), sleepiness or drowsiness ($p=0.000$), and arrhythmia or tachycardia ($p = 0.003$). Pfizer vaccine was associated with lower rates of fever, joint pain, lower limb edema, nausea, abdominal pain, sweating, distal limb tingling, vertigo, drowsiness, and tachycardia. AstraZeneca vaccine was associated with lower rates of chest pain.

In our study, fever was most commonly caused by Moderna vaccines (68.5%) and AstraZeneca (67%), whereas it was lower among the Pfizer group (58.3%). The association was deemed significant ($p= 0.001$). Fever and chills were also recorded as adverse reactions, with a greater prevalence in our trial than in a prospective observational study undertaken in the UK with the injection of the Astra Zeneca vaccine (Menni et al., 2021). Furthermore, half of the individuals who got either the AstraZeneca or Pfizer vaccinations had headaches (Kadali et al., 2021b; Kim et al., 2021; Riad et al., 2021b). Goldberg et al., (2021) conducted prospective research in the UK and discovered that systemic side effects, such as headache and tiredness, affected fewer than one in four participants and were less prevalent in the population than clinical studies predicted. In phase 3 clinical trials of the BNT162b2 vaccine3, for example, injection-site discomfort (71–83%), tiredness (34–47%), and headache (25–42%) were the most prevalent effects after the first dose. In a real-time analysis, the most common adverse effect of the Pfizer vaccination was headache (Kadali et al., 2021b). These results, however, were similar to ours for AstraZeneca vaccines but not for Pfizer vaccines. However, the relationship between headache and type of vaccine was not significant in our study.

After the first dosage, less than 30% of users experienced injection-site discomfort, and less than 25% reported weariness and headache, according to the research. Although adverse effects were much more common in women than in males, in persons aged 55 years or younger than in those older than 55 years, and after the second dosage than after the first dose, they occurred at far lower rates than the available literature predicted (Goldberg et al., 2021). In the study of Omeish et al., (2022) AstraZeneca had a higher rate of reported chest pain (8.7%) for the first dose, whereas it was higher in Pfizer vaccines for the second dose. In our study, the Moderna vaccine was associated with higher chest pain rates than Pfizer and AstraZeneca ($p = 0.000$).

Limitations of our research were based on an online questionnaire, which might result in selection bias. Despite this, online web-based surveys have been shown to be a cost-effective approach for representing the whole population and reaching persons who are difficult to reach (Fenner et al., 2012). This will make it easier for Saudi citizens to access social media sites, which were increasingly utilized as a source of information during the COVID-19 pandemic (Yassin et al., 2021). Over half of the people who took part (52.4%) had taken their last dose more than four months before they took part. This can lead to recall bias.

5. CONCLUSION

This study analysed the self-reported untoward effects associated with COVID-19 vaccines utilized in Saudi Arabia. The most reported side effects were fatigue, injection site swelling, headache, fever, drowsiness, joint and muscle pain, and decreased sleep quality. Pfizer vaccine was associated with lower rates of fever, joint pain, lower limb edema, nausea, abdominal pain, sweating, distal limb tingling, vertigo, drowsiness, and tachycardia. AstraZeneca vaccine was associated with lower rates of chest pain.

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Author Contributions

Authors contributed equally to the review of the current literature, questionnaire synthesis, data collection in snowball sampling technique, and manuscript writing.

Ethical approval

The ethical research committee of the Institutional Review Board (IRB) of Asir Health Administration, Abha, Saudi Arabia, approved this study (H-06-B-091, Rec-21-03-2020).

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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