MEDICAL SCIENCE

The impact of vaccination status on the severity of pain syndrome in COVID-19 patients of Al-Rayan Colleges, Al Madinah

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ABSTRACT

COVID-19 has a wide range of clinical features, of which pain syndrome is commonly met. Vaccination of COVID-19 reduced symptomatic infections and/or high viral load infection. The aim of this study is to compare the severity of pain syndrome among COVID-19 immunized and non-immunized patients in Al-Rayan Colleges, Al-Madinah. A retrospective cross-sectional observational study was carried out on 304 COVID-19 patients of age ranging from 18-65 years in AL-Rayan Colleges, AL-Madinah, KSA, between September 2021 to April 2023. An electronic questionnaire with 20 items was introduced to the participants of the study after filling in written consent. According to vaccine status, the participants of the study were divided into 5 groups; unvaccinated, partially vaccinated (≥ 14 days after dose 1 or < 14 days after dose2), Fully vaccinated (≥ 14 days after dose 2), 3rd dose vaccinated and 4th dose vaccinated. Pain syndrome symptoms were observed in all vaccinated and non-vaccinated participants with insignificant differences (P>0.05). Severe pain was highly observed in non-vaccinated participants (40.2%). While it was not detected (0%) in the 4th dose vaccinated group. It was (29.7%), (38.7%) and (39.1%) in partially vaccinated, fully vaccinated, and 3rd dose vaccine groups, respectively. In conclusion, pain syndrome was detected in all COVID-19 patients, while pain severity significantly increased in non-vaccinated patients and was absent in patients who had received the 4th dose of the vaccine.

Keywords: COVID-19, vaccination, pain syndrome, Headache, Myalgia.

1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a severe infection that has invaded the global world since December 2019. The patients may suffer from flu-like manifestations or even present with respiratory failure (Ouassou et al., 2020). Detection of SARS-CoV-2 in the cerebrospinal fluid in some patients pointed

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to the possibility of being a neuroinvasive virus. In addition, SARS-CoV-2 was found in the brain autopsies of some RT-PCR-negative patients (Paniz-Mondolfi et al., 2020; Freij et al., 2020). Acute pain occurs as a sore throat or systemic pain (pain syndrome) in the form of headache, myalgia, neuropathic pain, or arthralgia. An explanation of this pain is either the neurotropic action of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or an autoimmune response to the virus (Berger, 2020; Guadarrama-Ortiz et al., 2020). Moreover, SARS–CoV-associated cytokine storm may share in the pathogenesis of myalgia, headache, and arthralgia (Mangalmurti and Hunter, 2020).

Myalgia, elevated serum creatine kinase (CK) levels, and rhabdomyolysis are clues for virus-associated myositis in about one-third of patients (Fan et al., 2006; Wang et al., 2004; Chen et al., 2005; Tsai et al., 2004). Arthralgia is one of the possible early side effects that affect 10-15% of COVID-19 patients (Hoong et al., 2021). Headache is frequently met in COVID-19 patients, the mechanism of which is attributed to virus-related cytokines where the virus invades trigeminal nerve endings in the nasal cavity that, leads to endothelial damage, which initiates a vasoconstrictor and oxidative stress on the trigeminal nerve and hens induces headache (Bolay et al., 2020; Varga et al., 2020). During the COVID-19 pandemic, Multiple COVID-19 vaccines were approved by regulatory authorities and WHO as Emergency Use Listing or Emergency Use Authorization (EUL or EUA) according to randomized controlled trials on the vaccine's efficacy (Bio, 2021). mRNA (BNT162b2) COVID-19 vaccine is introduced in 2 doses (30 μg, 0.3 ml each with 4-8 weeks in between. Then 4-6 months later, the first booster dose is given. The second booster dose is introduced 4-6 months after the first booster dose mainly for immunocompromised.

Vaccination works against virus variants, but the effectiveness against severe and mild disease after two doses is lower for the Omicron variant than Delta, and waning is faster (World Health Organization, 2021). The recommended dosage for the ChAdOx1-S vaccine is two intramuscular doses (0.5ml each) 8 to 12 weeks apart. A booster dose may be given 4-6 months later with priority to immunocompromised individuals (World Health Organization, 2022). The way through which vaccination fights against the virus may be via stimulation of immunologic response with subsequent reduction of viral replication and getting rid of virus-infected cells (Ferdinands et al., 2021). Vaccination against COVID-19 with either BNT162b2 or ChAdOx1-S provides a significant decrease in symptomatic Covid-19 in older adults and reduces the severity of the disease (Bernal et al., 2021). We conducted this study to assess pain syndrome in COVID-19 patients and to find the possible changes in pain severity according to vaccine status in Al-Rayan Colleges, Al-Madinah.

2. METHODS

This retrospective cross-sectional observational study included 304 COVID-19 patients. The age of the participants was between 18-65 years. The study was carried out in AL-Rayan Colleges, AL-Madinah, KSA, in the period between September 2021 to April 2023. The infection of COVID-19 was confirmed by using reverse transcription-polymerase chain reaction (RT-PCR) with oropharyngeal and nasal swab samples. Open Epi calculated the sample size; in a previous study, http://www.openepi.com, according to the prevalence of pain syndrome in COVID-19 patients (Oguz-Akarsu et al., 2022). Data was collected through an electronic form of 20 items validated questionnaire. The questionnaire was sent to the study participants via email after completing the consent statement form.

The questionnaire included a query of age, gender, job, cigarette smoking, history of chronic diseases, COVID vaccination, the onset and duration of COVID infection, the vaccination status at infection, the duration between infection and the last vaccination dose, the need for hospital admission, treatment with oxygen therapy or ventilation, the presence and severity of neuropathic pain, myalgia, polyarthralgia, and headache. The intensity of pain was calculated according to the pain scale (Wong and Whaley, 1986). The questionnaire included an inquiry on elements of pain syndrome, neuropathic pain as defined by the International Association for the Study of Pain (Raja et al., 2020). Patients with indeterminate vaccination status (<14 days after dose 1) and chronic musculoskeletal disorders or chronic pain syndrome before the onset of COVID-19 infection were excluded. According to vaccine status, the participants of the study were divided into five groups; unvaccinated, partially vaccinated (≥14 days after dose one or < 14 days after dose 2), Fully vaccinated (≥ 14 days after dose 2), 3rd dose vaccinated and 4th dose vaccinated (Thompson et al., 2021).

Statistics methods

Data were statistically analyzed using SPSS version 20. Qualitative data were presented as Numbers and percentages using the Chi-square test. P value < 0.05 was considered significant.

3. RESULTS

The study included 304 participants, 230 (75.7%) were females. The age range is between 18-65 years. The severity of pain was significantly (P< 0.05) noticed in females (39.1%) while in males (27%). The pain severity was insignificantly higher (P> 0.05) in patients with chronic diseases (40%) compared to other patients (35.1%). There was no significant difference (P> 0.05) in pain severity between smokers (31.6%) and nonsmokers (31.7%). Severe pain was insignificantly higher (P> 0.05) in older patients (58-65 years) (44.4%).

All patients suffered from one or more symptoms of pain syndrome with insignificant differences (P> 0.05). The occurrence of myalgia was (74.7% and 82.8%) in non-vaccinated and partially vaccinated individuals, respectively. In the fully vaccinated patients, myalgia was reported in (80%) while, there was some decrease in the 3rd dose vaccine group (72.5%) and in the 4th dose vaccine group (44.4%). Headache presented in (85.1%) of non-vaccinated and (90.6%) of partially vaccinated groups. It was (85.3%) of fully vaccinated participants. In 3rd dose vaccine and 4th dose vaccine groups it was (84.1% and 66.7%, respectively). Neuropathic pain affected (24.1%), (32.8%), 29.3%, and (30.4%) of non-vaccinated, partially vaccinated participants, fully vaccinated, and 3rd dose vaccine patients, respectively. While 4th dose vaccine group showed the lowest percentage (11.1%) (Table 1) (Figure 1).

Table 1 Pain symptoms in the study groups.

Vaccine status	Pain symptom				Total 304
	Myalgia	Headache	Neuropathic Pain	Polyarthralgia	
Non-vaccinated	65 74.7%	74 85.1%	21 24.1%	57 65.5%	87
Partially vaccinated	53 82.8%	58 90.6%	21 32.8%	42 65.6%	64
Fully vaccine	60 80%	64 85.3%	22 29.3%	47 62.7%	75
3rd dose vaccine	50 72.5%	58 84.1%	21 30.4%	39 56.5%	69
4th dose vaccine	4 44.4%	6 66.7%	1 11.1%	2 22.2%	9
P value	0.099	0.397	0.576	0.104	

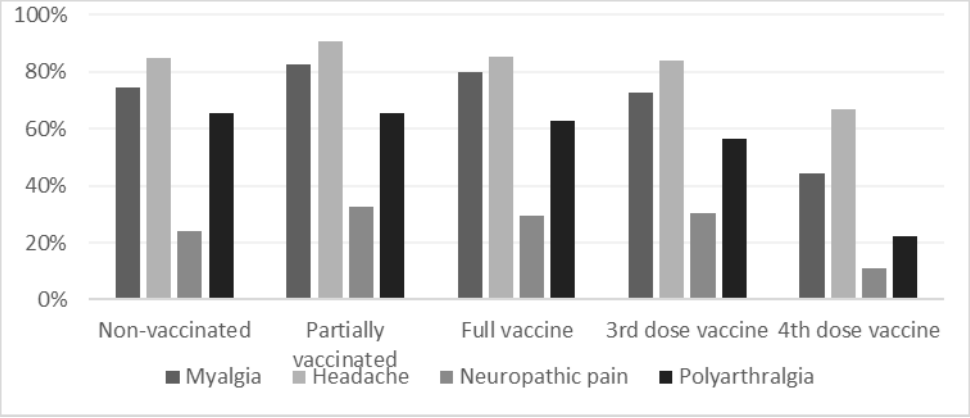

Figure 1 Pain symptoms, myalgia, headache, neuropathic pain, and polyarthralgia were observed in all study participants with insignificant differences.

The severity of pain differs significantly (P<0.05) in all groups. Severe pain was highly observed in non-vaccinated participants (40.2%) and not detected (0%) in the 4th dose vaccinated group. It was (29.7%), (38.7%) and (39.1%) in partially vaccinated, fully vaccinated, and 3rd dose-vaccinated groups, respectively (Table 2) (Figure 2).

Table 2 Pain severity in study groups.

Vaccination status	Pain severity					P-value
	No pain	Mild	Moderate	Severe	Total	
Non- vaccinated	9	10	33	35*	87	
%	10.3%	11.5%	37.9%	40.2%	100%	
Partially- vaccinated	2	14	29	19*	64	
%	1.3%	21.9%	45.3%	29.7%	100%	
Fully vaccinated	3	17	26	29*	75	
%	4%	22.7%	34.7%	38.7%	100%	
3rd dose vaccine	11	16	15	27*	69	
%	15.9%	23.2%	21.7%	39.1%	100%	<0.05
4th dose vaccine	4	5	0	0*	9	
%	44.4%	55.6%	0%	0%	100%	

*P < 0.05

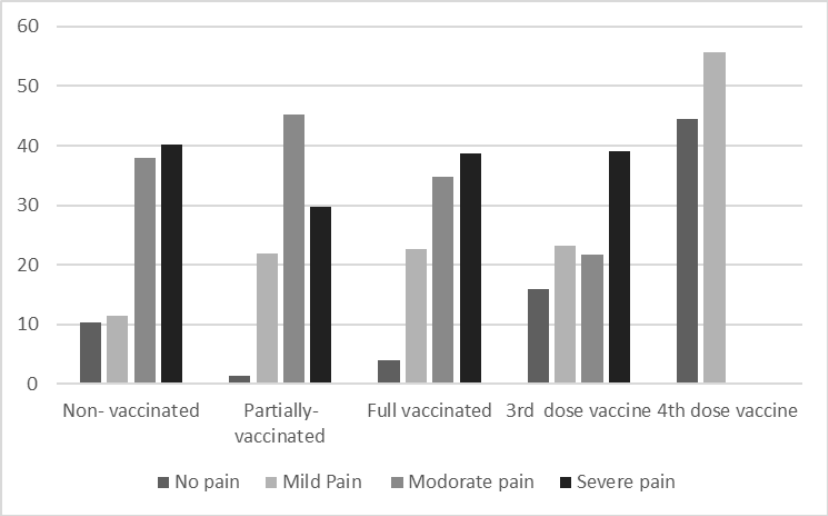

Figure 2 Pain severity differs significantly among all study groups. It was highest in non-vaccinated patients.

4. DISCUSSION

This study was conducted as a trial to assess pain syndrome in COVID-19 patients and to find the possible changes in pain severity according to vaccine status. The symptoms of pain syndrome in the form of myalgia, headache, neuropathic pain, and arthralgia were detected in all participants. Similar findings were demonstrated in a study where musculoskeletal manifestations were study observed in 88 (30%) of 294 hospitalized COVID-19 patients. 37.5% of this manifestation was myalgia with the more severe presentation, 5.7% arthralgia, 6.8% new-onset backache, and 50% generalized body ache (Hoong et al., 2021). In another study on 222 COVID-19 patients, 159 patients had one or more pain syndrome symptoms (71.6%). 110 (49.6%) patients had myalgia, headache was reported in 109 (49.1%), neuropathic pain in 55 (24.8%), and polyarthralgia in 30 (13.5%) patients (Oguz-Akarsu et al., 2022). In this work, pain severity was insignificantly higher in older participants and patients with chronic diseases.

Similar data were obtained by a retrospective study on 167,500 participants where comorbidities and old age were associated with a higher risk of COVID severity (Ge et al., 2021). The severity of pain was significantly observed in female participants, which differs from another study, where the male gender was associated with pain severity (Jena et al., 2022). These findings may be attributed to the higher number of female participants in this study. Similarly, fewer male participants explain the insignificant pain severity in smoker patients. Despite detecting an association between smoking and pain severity in COVID infection in previous studies (He et al., 2022; Gülsen et al., 2020). COVID-19 vaccination is supposed to ameliorate both the severity and the duration of infection (Tran et al., 2023). Although pain syndrome was reported in all study participants, the severity of pain showed a significant difference in all groups. Severe pain was highly observed in non-vaccinated participants.

On the other hand, it was not detected in the 4th-dose vaccinated group. These results pass parallel with the findings of a prospective cohort study on 204 participants to compare COVID-19 vaccine effectiveness on vaccinated and non-vaccinated individuals. The mean viral RNA load and the risk of febrile symptoms were lower in vaccinated (fully or partially vaccinated) than in unvaccinated individuals. In addition, shorter illness time occurred more in vaccinated compared to unvaccinated patients (Thompson et al., 2021). Another study assumed that the efficacy of the COVID-19 vaccine to alleviate the severity of the disease diminished from 1 month to 6 months after full vaccination. The efficacy against infection and symptomatic disease showed a 20-30% reduction by six months (Feikin et al., 2022).

The relatively high expression of severe pain in fully vaccinated and 3rd dose-vaccinated groups may be due to different vaccine types and post-vaccination time on vaccine effectiveness. This fact was illustrated in a study investigating the efficacy of the COVID-19 vaccine in protecting against severe infection. Booster mRNA vaccine protection against severe COVID-19 was achieved more by three-dose inactivated SARS-CoV-2 vaccination than by 2-dose, while less protection was observed in the 3-dose mRNA COVID-19 vaccine (Ng et al., 2022). In addition, infection with COVID-19 variants may add to the weaning of vaccine effectiveness with time. Andrews et al., (2022) concluded that vaccine effectiveness against symptomatic COVID-19 with the delta variant diminished to 44.3% by three months after the second dose with the ChAdOx1-S vaccine and to 66.3% with the BNT162b2 vaccine.

Furthermore, fading of vaccine 3rd dose effectiveness with time was illuminated in another study. Where vaccine effectiveness after taking both 2 and 3 doses of mRNA vaccine was lower during the Omicron compared to the Delta variant period. The effectiveness against COVID-19–associated emergency department/urgent care (ED/UC) visits and hospitalizations was 87% and 91%, respectively in 2 months interval and lowered with time to 66% and 78% by the 4th month (Ferdinands et al., 2022). This study has several limitations. We did not investigate the factors which affect the weaning of vaccine effectiveness such as time, immunity status, and vaccine product.

This study did not differentiate between the reason for the third dose either an additional dose for immunocompromised or as a booster dose after completion of a primary series in immunocompetent individuals. That may affect the vaccine's effectiveness against severe pain. Genetic characterization of the virus was not available, which is necessary for variant detection with possible alteration of vaccine effectiveness. Further research with a larger sample size that will consider these points is needed. Despite the apparent leaving specter of COVID-19 infection, after attacking the earth for several years with millions of victims, it deserves diligent research for double its catastrophic time to solve its secrets and to guard against possible other attacks.

5. CONCLUSION AND RECOMMENDATIONS

pain syndrome was presented in all COVID-19 patients while, pain severity significantly increased in non-vaccinated patients and was absent in patients who had received the 4th dose of the vaccine. More studies are needed to further analyze of vaccine effectiveness determinants against COVID-19 severity.

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Author Contributions

SE designed and supervised the study. LA, TA performed data collection. GN analyzed the results and statistical data. All authors contributed to the writing and approved the final draft.

Ethical approval

The Medical Ethics Committee of AL Rayan Colleges (HA-03-M-122) approved the study.

Informed consent

Written informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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