A Cross-Sectional Analysis of Muscular and Joint Symptoms in COVID-19 Patients: Insights from Syria.

Introduction:

Since its emergence in 2020, Coronavirus Disease 2019 (COVID-19) has radically transformed lifestyles and exerted immense pressure on public health infrastructures worldwide1. Not merely confined to respiratory ailments, COVID-19 exhibits a plethora of manifestations, notably in the musculoskeletal system. Such symptoms can linger for weeks or even months, predominantly in severe and critical cases of the infection [1-3].

The underlying mechanisms behind the virus's adverse effects on muscle tissue can be attributed to two prevailing hypotheses. The first proposes a direct binding of the virus to the ACE2 receptor on muscle cell surfaces, leading to muscle weakness. The second postulates that the heightened inflammatory response triggered by the virus adversely impacts musculoskeletal tissues. This reaction releases cytokines, which can induce multi-organ injuries, manifesting chiefly as fatigue and myalgia [4-6]. Additionally, factors like prolonged immobilization during illness or pre-existing autoimmune, neuromuscular, and muscular conditions might exacerbate musculoskeletal symptoms [4-6].

Musculoskeletal symptoms and their disparities among sexes are areas warranting more attention. Although males present an increased risk of severe COVID-19 outcomes and higher infectivity rates than females [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9149780/], women with severe symptoms have demonstrated elevated levels of IgG antibodies against SARS-CoV-2 and a stronger early-phase antibody response[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9149780/]. Moreover, female gender associates significantly with the long COVID syndrome [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8575536/]. Nevertheless, another study observed comparable symptoms and comorbidities between the genders [https://www.frontiersin.org/articles/10.3389/fpubh.2020.00152/full]. These disparities could arise from various socio-health determinants like smoking habits or mask-wearing compliance and biological factors, given the well-established differences in the immune systems of both sexes.

Numerous studies have documented an array of musculoskeletal symptoms in COVID-19 patients. Fatigue, which can be enduring, arthralgia, arthritis, myalgia, myositis, rhabdomyolysis, and myopathy are among the most commonly reported. These

symptoms can profoundly affect patients' quality of life, potentially triggering anxiety and depression[4,7-9].

Regrettably, only a handful of laboratory and imaging techniques delve into the musculoskeletal ramifications of COVID-19. Yet, their insights are invaluable. These findings play a pivotal role in the assessment, diagnosis, and prognosis of musculoskeletal manifestations, subsequently guiding the therapeutic journey[10-11].

It is worth noting that drugs such as corticosteroids, colchicine, and hydroxychloroquine, which find utility in the treatment of COVID-19, might be double-edged swords. Their potential side effects, including myalgia, myopathies, myositis, and arthralgia, can mimic the very symptoms of COVID-19, necessitating judicious clinical discernment[12-13].

Empirical data has shed light on the prominence of muscle symptoms among hospitalized patients during SARS-CoV-2's acute phase. Manifestations like myalgia, evident muscle wasting, myopathy, rhabdomyolysis, and elevated serum CK levels were more frequent among severe cases. Conversely, a minor 5.12% to 2.36% of mild COVID-19 cases reported fatigue, myalgia, and weakness [14-16]. A review of available literature identified thirteen studies that highlighted persistent muscle-related symptoms, even in non-hospitalized individuals with milder infection variants. These primarily include fatigue, deteriorated quality of life, prolonged arthralgia, and persistent myalgia [17-19].

Therefore, this research endeavors to explore the recurrent effects of COVID-19 infections on the musculoskeletal symptoms both during and post-infection among the Syrian population. Additionally, we seek to investigate any disparities in these musculoskeletal symptoms between males and females. Through this inquiry, we aim to bridge gaps in understanding and provide insights to better manage and treat affected individuals.

Methods:

Study Design and Rationale:

This was a cross-sectional study conducted between June and October 2022 at Al-Mouassa University Hospital, Damascus, Syria. The rationale for employing a cross-sectional design was twofold: it permitted an assessment of musculoskeletal manifestations in COVID-19 patients at a singular, crucial time point - both during their infection and post-infection. Moreover, given the rapidly evolving nature of the COVID-19 pandemic, this design enabled timely data collection, essential for generating hypotheses about musculoskeletal symptoms' underlying mechanisms or potential

prolonged effects. This study protocol received approval from the Ethical Committee of the Mouassat Hospital. Furthermore, in line with the Helsinki Declaration, all participants rendered written informed consent before their involvement.

Study Population and Sampling:

A total of 1039 participants, all aged above 18 years and residing in Damascus, were recruited. The recruitment combined online survey dissemination and field recruitment to mitigate potential biases. Online, 625 participants completed the questionnaire after it was shared on various websites and social media platforms. For field recruitment, 414 participants were approached at Al-Mouassa University Hospital outpatients clinics and at Faculty of Medicine, Damascus University. After a thorough explanation of the study's objectives, willing patients were provided an online survey link and monitored during completion.

Inclusion and Exclusion Criteria:

Inclusion: Participants aged ≥ 18 years with a prior COVID-19 infection or suspicious COVID-19 infection and currently residing in Damascus.

Exclusion: Participants below 18 years, those unwilling to give consent, individuals with joint surgery history, pregnant women, or those who had taken immunosuppressive drugs before the study.

Data Collection:

The primary tool was an adapted questionnaire based on the study 'Musculoskeletal symptoms and related factors in post-acute COVID-19 patients [20]. This questionnaire underwent modifications to tailor it to our participants, specifically emphasizing clarity and comprehension. Though budget constraints restricted laboratory tests such as PCR, CRP, and WBC, the adapted questionnaire captured inflammation-related symptoms, such as musculoskeletal swelling and pain. Comprehensive, interviewer-administered questionnaires solicited data on demographic, social, clinical, and behavioral aspects, alongside specifics like vaccination status, musculoskeletal symptoms during and post COVID-19 infection, and rheumatoid disease status.

Outcome Measures:

The primary outcome measure of this study was the prevalence and nature of musculoskeletal manifestations in individuals with past COVID-19 infections. Secondary

outcome measures included factors influencing these manifestations, such as vaccination status, and potential associations with conditions like osteoporosis

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 28.0.0.0. Continuous variables were depicted as both means with standard deviations and medians with their respective ranges. Categorical variables were presented in terms of frequencies and associated percentages.

For the comparison of categorical variables, the Chi-Square test was utilized. Continuous variables were evaluated using the Mann-Whitney U test to determine significant differences between groups. A threshold of $p < 0.05$ was set for statistical significance. Findings were systematically organized and exhibited in tables or graphical representations as deemed fitting.

Results:

Demographics and Clinical Characteristics of the Participants:

The demographic distribution, summarized in Table 1, elucidated certain distinctive trends in our study population. Of the 1,039 participants, 613 (59.0%) were females, and 426 (41.0%) were males. The age range spanned 18 to 78 years, with a similar median age observed in females (25 years) compared to males (24 years); this difference was statistically significant ($p=0.018$). Most participants resided in urban areas, accounting for 82.8% of the total, with no significant gender-wise disparity noted. When evaluating marital status, a striking difference was evident: a larger proportion of males (78.4%) were single compared to females (67.2%), and this difference was statistically significant ($p<0.001$).

Turning our attention to the participants' COVID-19 experiences, the majority had encountered the infection once (60.6%). The recurrence of infections did not significantly differ between genders. Interestingly, the severity of the first infection revealed that a vast majority, 85.2%, experienced low severity, but a significant difference was noted in the distribution between males and females ($p=0.018$). Males appeared to exhibit a higher prevalence of asymptomatic cases during their first infection (13.4%) than females (8.0%) (Table 1).

Regarding the diagnostic approaches for COVID-19, the most common method for both genders was based on symptom presentation (62.5%), with no significant differences observed in the utilization of rapid tests or PCR. As for the vaccination status against COVID-19, slightly over half of the participants, 55.2%, had been vaccinated, with males (56.3%) having a marginal lead over females (54.5%), though this difference was not statistically significant (Table 1).

Table 1: Demographic characteristics of the participants

		Female (n=613)	Male (n=426)	Total (n=1039)	P-Value
Age	**Median (Range)**	25 (18-78)	24 (18-77)	24 (18–78)	0.018*
	Mean ± SD	29.4 ± 11.2	29.0 ± 12.9	29.27 ± 11.9	
Residual area	**Rural**	112 (18.3%)	67 (15.7%)	179 (17.2%)	NS
	City	501 (81.7%)	359 (84.3%)	860 (82.8%)	
Social Status	**Single**	412 (67.2%)	334 (78.4%)	746 (71.8%)	<0.001*
	Married	181 (29.5%)	80 (18.8%)	261 (25.1%)	
	Divorced	10 (1.6%)	9 (2.1%)	19 (1.8%)	
	Widow	10 (1.6%)	3 (0.7%)	13 (1.3%)	
Number of times of COVID-19 Infections	**Once**	376 (61.3%)	254 (59.6%)	630 (60.6%)	NS
	Twice	171 (27.9%)	132 (31.0%)	303 (29.2%)	
	Three times	52 (8.5%)	28 (6.6%)	80 (7.7%)	
	More than that	14 (2.3%)	12 (2.8%)	26 (2.5%)	

COVID-19 infection Now	**Yes**	16 (2.6%)	15 (3.5%)	31 (3.0%)	NS
	No	581 (94.8%)	407 (95.5%)	988 (95.1%)	
	Maybe	16 (2.6%)	4 (0.9%)	20 (1.9%)	
Severity of the First infections	**Low**	534 (87.1%)	251 (82.4%)	885 (85.2%)	0.018*
	Severe	30 (4.9%)	18 (4.2%)	48 (4.6%)	
	No symptoms	49 (8.0%)	57 (13.4%)	106 (10.2%)	
The severity of the symptoms in recurrent infections	**Lower**	117 (19.1%)	107 (25.1%)	224 (21.6%)	NS
	More severe	59 (9.6%)	48 (11.3%)	107 (10.3%)	
	Same	82 (13.4%)	49 (11.5%)	131 (12.6%)	
	Only one infection	355 (57.9%)	222 (251%)	577 (55.5%)	
COVID-19 diagnostic way	**Rapid test**	79 (12.9%)	65 (15.3%)	144 (13.9%)	NS
	PCR	154 (25.1%)	93 (21.6%)	246 (23.7%)	
	Symptoms	380 (62.0%)	269 (63.1%)	649 (62.5%)	
Taken COVID-19 vaccines	**Yes**	334 (54.5%)	240 (56.3%)	574 (55.2%)	NS
	No	279 (45.5%)	186 (43.7%)	465 (44.8%)	

Vaccine Distribution among Participants

Delving into the types of COVID-19 vaccines received by the participants, Table 2 illustrates a diverse range of choices. AstraZeneca and Pfizer emerged as the most preferred vaccines, accounting for 31% and 30.3% of the vaccinated participants, respectively. Other vaccines like Sputnik and Sputnik Light were also fairly common, with uptake rates of 11.7% and 12.4% respectively. Notably, 12.0% of the participants reported having received two different types of vaccines.

Table 2: Types of Vaccines	
AstraZeneca	178 (31%)
Johnson	28 (4.9%)
Moderna	32 (5.6%)
Pfizer	174 (30.3%)
Sinopharm	53 (9.2%)
Sinovac	27 (4.7%)
Sputnik	67 (11.7%)
Sputnik light	71 (12.4%)
Not known	16 (2.8%)
2 different types	69 (12.0%)

Muscular and Joint Symptoms by Sex

Table 3 presents a comprehensive comparison of muscle and joint symptoms among the participants, segmented by sex. During their COVID-19 infection, muscle-related symptoms were prominent among both genders, with 71.6% of females and 73.0% of males reporting them. Specifically, muscle pain was the dominant symptom, reported by 70.4% of the symptomatic females and 66.9% of the symptomatic males. Malaise and fatigue were also non significant, affecting 27.6% of the symptomatic females and 30.9% of the symptomatic males. A smaller fraction experienced an inability to perform certain movements, at 7.7% for females and 5.8% for males.

As for joint-related symptoms during the infection, 38.5% of females and 42.0% of males reported experiencing them. Of these, joint pain was overwhelmingly the most prevalent complaint, reported by 90.7% of symptomatic females and 88.8% of symptomatic males. Limitations in joint movement were described by 15.7% of symptomatic females and 19.6% of symptomatic males. Swelling and tenderness of joints were relatively less common but were still observed in 7.2% of symptomatic females and 8.9% of symptomatic males.

Interestingly, post-infection muscle symptoms were reported by approximately 30% of both genders, with both groups equally experiencing muscle pain (59.4%). Similarly, malaise and fatigue post-infection were reported by 55.1% of symptomatic females and 54.7% of symptomatic males. Joint symptoms post-infection were found in 19.9% of females and 19.2% of males, with joint pain being the most common complaint.

Table 3: Muscle and joints symptoms among the participants compared by sex

		Female (n=613)	Male (n=426)	Total (n=1039)	P-Value
Symptoms during the	**Muscles Symptoms**	**439 (71.6%)**	**311 (73.0%)**	**750 (72.2%)**	**NS**

COVID infections	**1) Muscle Pain**	309 (70.4%)	208 (66.9%)	517 (68.9%)	NS
	2) Malaise and Fatigue	121 (27.6%)	96 (30.9%)	217 (28.9%)	NS
	3) Inability to do some movement	34 (7.7%)	18 (5.8%)	5.2 (6.9%)	NS
	<u>Joint Symptoms</u>	**<u>236 (38.5%)</u>**	**<u>179 (42.0%)</u>**	**<u>415 (39.9%)</u>**	**<u>NS</u>**
	1) Joint swallow and tenderness	17 (7.2%)	16 (8.9%)	33 (8.0%)	NS
	2) Joint Pain	214 (90.7%)	159 (88.8%)	373 (89.9%)	NS
	3) Limitation in joint movement	37 (15.7%)	35 (19.6%)	72 (17.3%)	NS
Symptoms Post COVID infections	**<u>Muscles Symptoms</u>**	**<u>175 (30.5%)</u>**	**<u>295 (30.0%)</u>**	**<u>315 (30.3%)</u>**	**<u>NS</u>**
	1) Muscle Pain	111 (59.4%)	76 (59.4%)	187 (59.4%%)	NS
	2) Malaise and Fatigue	103 (55.1%)	70 (54.7%)	173 (54.9%)	NS
	3) Inability to do some movement	19 (10.2%)	11 (8.6%)	30 (9.5%)	NS
	<u>Joint Symptoms</u>	**<u>122 (19.9%)</u>**	**<u>82 (19.2%)</u>**	**<u>204 (19.6%)</u>**	**<u>NS</u>**
	1) Joint swallow and tenderness	12 (9.8%)	12 (14.6%)	24 (11.8%)	NS

	2) Joint Pain	90 (73.8%)	65 (79.3%)	155 (76.0%)	NS
	3) Limitation in joint movement	18 (14.8%)	11 (13.4%)	29 (14.2%)	NS

The revised Table 4 showcases the prevalence of specific joint afflictions experienced during COVID-19 infections, broken down by gender. The knee joint was the most commonly affected for both females (22.9%) and males (28.5%). For females, the subsequent most commonly affected joints were the shoulder (13.1%) and hip (16.9%). For males, the hip (19.0%) and feet (11.7%) followed the knee in prevalence. It is noteworthy that across all joint types, the differences in prevalence between females and males were not statistically significant, as indicated by the non-significant p-values.

Table 4: Prevalence of Specific Joint Afflictions During COVID-19 Infection by Sex

		Female (n=236)	**Male (n=179)**	**Total (n=415)**	**P-Value**
Joint Type	**Hip**	40 (16.9%)	34 (19.0%)	74 (17.8%)	NS
	Knee	54 (22.9%)	51 (28.5%)	105 (25.3%)	NS
	Elbow	12 (5.1%)	12 (6.7%)	14 (5.8%)	NS
	Feet	24 (10.2%)	21 (11.7%)	45 (10.8%)	NS
	Shoulder	31 (13.1%)	23 (12.8%)	54 (13.0%)	NS
	Neck	19 (8.1%)	14 (7.8%)	33 (7.9%)	NS
	Ankle	18 (7.6%)	16 (8.9%)	34 (8.2%)	NS

Sex-Specific Overview of Joint Symptomatology in COVID Cases:

Table 5 presents a detailed breakdown of joint symptom characteristics observed during COVID-19 infections, segmented by gender and the entire cohort. Regarding the number of joints affected, a vast majority of participants, 74.0% overall, reported no joint afflictions. When joints were affected, 7.1% of the participants experienced issues in one joint, with 13.1% reporting afflictions in fewer than four joints, and 5.8% mentioning issues in more than four joints. The prevalence of these symptoms was fairly consistent between both genders, as indicated by the non-significant p-values.

As for the duration of the joint pain, 5.5% of the participants suffered for more than 6 months, while 30.3% reported pain lasting less than 6 months. Again, the distribution of durations was comparable between females and males. Additionally, 5.7% of the participants had associated rheumatoid diseases, with a slightly higher prevalence in males (6.8%) than in females (4.9%). Lastly, 3.3% of the entire group had been diagnosed with osteoporosis following the COVID vaccine, with a slightly higher incidence in males (3.5%) compared to females (3.1%). Across all metrics discussed, the differences between males and females did not attain statistical significance.

Table 5: Comparison of Joint Symptoms' Duration and Related Diseases by Sex

		Female (n=613)	Male (n=426)	Total (n=1039)	P-Value
Number of Joints affected	**One Joint**	42 (6.9%)	32 (7.5%)	74 (7.1%)	NS
	Less Than 4	80 (13.1%)	56 (13.1%)	136 (13.1%)	
	More Than 4	34 (5.5%)	26 (6.1%)	60 (5.8%)	
	No Joints	457 (74.6%)	312 (73.2%)	769 (74.0%)	
Duration of Joint Pain	**More than 6 months**	33 (5.2%)	25 (5.9%)	58 (5.5%)	NS

	Less than 6 months	185 (30.2%)	130 (30.5%)	315 (30.3%)	
Rheumatoid Diseases		30 (4.9%)	29 (6.8%)	59 (5.7%)	NS
Have you been diagnosed with osteoporosis after the COVID vaccine		19 (3.1%)	15 (3.5%)	34 (3.3%)	NS

Discussion:

The study, involving 1,039 participants, unveiled distinct demographic trends and COVID-19 experiences, with 59.0% females and significant gender-based differences in marital status. Urban residency was predominant, and 60.6% encountered COVID-19 once. Symptom-based diagnostics and vaccination (55.2%) favored AstraZeneca and Pfizer. Muscular and joint symptoms, prevalent during and post-COVID, showed no significant gender differences, and knee joints were most commonly affected. AstraZeneca and Pfizer dominated vaccine distribution. Despite these observations, the differences in symptom presentation and prevalence between genders did not attain statistical significance in most metrics. This comprehensive insight into the clinical progression of COVID-19 and its aftermath among our cohort provides a foundation for further discussions on symptom management and long-term care.

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Hold significant implications for the broader landscape of public health in the post-pandemic era. The high occurrence of musculoskeletal symptoms, especially in the context of COVID-19, underscores the necessity for a comprehensive understanding of the enduring effects on the Syrian population. The study's thorough examination of gender-specific manifestations yields crucial insights for tailoring healthcare strategies.

Muscle and joint symptoms, prevalent both during and after COVID-19 infection, can profoundly impact individuals' quality of life, potentially resulting in prolonged discomfort and hindering daily activities. The study's acknowledgment of comparable prevalence between genders, despite minor variations, underscores the importance of inclusive health interventions. The identified differences in marital status and urban residence provide nuanced socio-demographic insights into the distribution and experiences of COVID-19 within the Syrian population. The varied distribution of COVID-19 vaccines, with AstraZeneca and Pfizer emerging as predominant choices, furnishes valuable information for healthcare planning and resource allocation. We found in this study that arthralgia and myalgia were to be the most common musculoskeletal manifestation during and post covid which is consistent with a study focused on Mechanisms of Musculoskeletal Pain in Long COVID(22).

Studies investigating the association between gender and musculoskeletal symptoms yielded mixed results. While a study in Iran found no sex differences [23], a study in Turkey reported higher prevalence in females [24], which aligns with our study, where the females were more symptomatic , but the difference did not reach statistical significance. This inconsistency might be due to methodological variations, including unequal sample sizes and potential confounders such as age, BMI, and education levels.

Existing literature proposes two dominant hypotheses: the direct binding of the virus to ACE2 receptors on muscle cells, inducing muscle weakness, and an inflammatory response that adversely affects musculoskeletal tissues, and this goes along with the A Narrative Review Article (25).

This heightened inflammatory reaction may lead to multi-organ injuries, manifesting in symptoms like fatigue, myalgia, and joint pain. Furthermore, factors such as prolonged immobilization during illness or pre-existing autoimmune, neuromuscular, and muscular conditions could potentially intensify musculoskeletal symptoms.

The cross-sectional design of the study inherently restricts its capacity to establish causation or unveil the dynamic evolution of musculoskeletal symptoms over time. The utilization of a convenience sample, amalgamating online survey distribution and field recruitment, may introduce selection biases. The study predominantly depends on self-reported data, potentially leading to recall bias and subjective interpretations of symptoms.

Conclusion

The study highlights a significant prevalence of musculoskeletal symptoms both during and after COVID-19 infection, with notable complaints such as muscle pain, joint pain, and fatigue. Importantly, these symptoms exhibit persistence post-infection, underscoring the need for sustained attention to comprehend their long-term impact on affected individuals. The dominance of AstraZeneca and Pfizer in Syria's vaccine landscape underscores the importance of understanding not only infection-related symptoms but also the potential musculoskeletal repercussions associated with different vaccines. In the face of the pandemic's repercussions on a global scale, this research advocates for a comprehensive approach to post-COVID-19 care in Syria, urging consideration not solely of respiratory complications but also of musculoskeletal symptoms, acknowledging their prevalence and potential contribution to long-term morbidity.

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