Journal of Taibah University Medical Sciences (2022) 17(2), 186–191

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com

Original Article

Frequency of orthopedic manifestations in COVID-19 patients

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Received 5 November 2021; revised 22 January 2022; accepted 2 February 2022; Available online 18 February 2022

الملخص

أهداف البحث: تم سابقا رصد تأثيرات الفيروس التاجي الجديد (كوفيد-19) على الجهاز العضلي الهيكلي مع تنوع كبير. الغرض من هذه الدراسة هو تحديد مدى انتشار الأعراض العضلية الهيكلية وما إذا كانت مرتبطة بخصائص المريض الأخرى.

طرق البحث: كانت هذه مراجعة بأثر رجعي لـ 685 مريضا منوما تبين أنهم مصابون بفيروس كوفيد-19 أثناء تنويمهم. استنادًا إلى استبيان كوفيد-19، سجلنا شكاوى من ظهور آلام عضلية جديدة وآلام المفاصل وآلام الظهر وضعف العضلات إضافة إلى مراجعة الرسم البياني لجميع الأمراض المصاحبة الحالية. تم إجراء التحليلات الإحصائية لتحديد العلاقة بين الأمراض المصاحبة المختلفة وأعراض العظام لمرضى كوفيد-19.

النتائج: من بين 685 مريضا ثبتت إصابتهم بكوفيد-19، أظهر 186 مريضا مظهرا واحدا على الأقل من أعراض أمراض العظام (27.1٪). كان المرضى الذين عانوا من أعراض العظام أصغر بشكل ملحوظ عند 53.7 سنة مقابل 58.1 مع مؤشر كتلة جسم أعلى بكثير عند 32.6 مقابل 30.0. المرضى الذين يعانون من مرض السكري أو يعانون من السمنة كانت لديهم معدلات أعلى بشكل ملحوظ من أعراض العظام في حين أن أولئك الذين يعانون من أمراض القلب أو الرئة لديهم معدلات أقل بشكل ملحوظ.

الاستنتاجات: يعاني مرضى السمنة ومرضى السكري من معدلات أعلى لأعراض العظام أثناء الإصابة بكوفيد-19. يجب إجراء المزيد من الدراسات في هذه الفئات لتحديد ما إذا كانت هذه الحالات الالتهابية أثناء العدوى لها تأثير على الجهاز العضلي الهيكلي في الأوقات المحيطة بالجراحة وبعد التعافي من العدوى.

الكلمات المفتاحية: كوفيد-19؛ مرض السكري؛ ألم عضلي؛ السمنة؛ جراحة العظام

Abstract

Objectives: The effects of the novel coronavirus on the musculoskeletal system have been reported with wide variability. The purpose of this study was to determine the prevalence of musculoskeletal symptoms and if these correlated with other patient characteristics.

Methods: This was a retrospective review of 685 admitted patients who were found to be positive for COVID-19 during their admission. Based on a standard COVID-19 questionnaire, we recorded complaints of new onset myalgias, joint pain, back pain, and muscle weakness and performed a chart review for all existing comorbidities. Statistical analyses were performed to determine the association between various comorbidities and orthopedic manifestations of COVID-19 patients.

Results: Of the 685 patients who tested positive for COVID-19, 186 patients presented with at least one orthopedic manifestation (27.1%). Patients that experienced orthopedic manifestations were significantly younger at 53.7 years of age compared to 58.1 years of age ($p = 0.003$) with a significantly higher BMI (body mass index) at 32.6 *versus* 30.0 ($p = 0.022$). Patients that had diabetes or were obese had significantly higher rates of orthopedic manifestations while those that had heart or lung disease had significantly fewer.

Conclusion: Obese and diabetic patients had significantly higher rates of orthopedic symptoms during COVID-19 infection. Further studies need to be carried out in these populations to determine if these comorbidities during infection have an effect on the musculoskeletal system in the perioperative setting and after recovery from infection.

Keywords: COVID-19; Diabetic; Myalgia; Obese; Orthopedic

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Peer review under responsibility of Taibah University.

ELSEVIER Production and hosting by Elsevier

 https://doi.org/10.1016/j.jtumed.2022.02.002

Introduction

The worldwide spread of the novel coronavirus, SARS-CoV-2, has left many questions relating to the pathophysiological and clinical course of COVID-19. Since its emergence, there has been discussion about the presentation of the virus and reports of various organ system manifestations. The clinical features of this disease range from asymptomatic patients to acute respiratory distress and multiple organ dysfunction, while the most common symptoms include fever, cough, and dyspnea. There has also been a number of musculoskeletal symptoms such as myalgia, arthralgia, and generalized muscle fatigue.[1] While these symptoms are not uncommon in viral infections, the extent to which this novel virus affects the musculoskeletal system is not fully understood as the literature remains limited with regards to the prevalence and relationship of these symptoms to various comorbidities.

Musculoskeletal manifestations in viral illnesses have been attributed to the inflammatory immune response through various cytokines, particularly interleukin (IL)-6 and tumor necrosis factor (TNF)-α.[2] The levels of IL-6 and TNF-α in both plasma and respiratory secretions have been directly correlated with the magnitude of severity in COVID-19 positive patients, particularly in patients with common comorbidities that may be further contributing to their increased inflammatory state.[3,4] Some recent studies also suggest that the mechanism behind COVID-19 myalgia may vary from the cytokine storm seen in typical viral infections. With an elevation of lactate dehydrogenase and the absence of creatine kinase, one study suggested that COVID-19 myalgias may be enhanced through a novel mechanism related to muscle ischemia rather than just cell death.[5]

Various comorbidities that lengthen the course of infection and increase the severity of disease may also play an exacerbating role in musculoskeletal symptoms (myalgia, arthralgia, etc.). Many comorbidities, such as type 2 diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease, are thought to cause chronic inflammation and an imbalance in immune regulation, particularly when under the load of a viral infection.[6,7] These patients are far more susceptible to COVID-19 complications as the virally-induced cytokine storm further intensifies the immune dysregulation and leads to worse outcomes.

Identifying which comorbidities are associated with increased musculoskeletal symptoms may provide benefit in the clinical estimation of disease progression. We know very little about the viral pathogenesis of COVID-19 and its effect on the musculature, or if there are concerns for orthopedic procedures in patients that have active or recent infection. Our purpose is to report the prevalence of musculoskeletal manifestations in COVID-19 patients and expose any relationships that may exist between various comorbidities and these symptoms.

Materials and Methods

This was a retrospective review of 685 admitted COVID-19 positive patients at a single institution. We included all patients that were found to be positive for COVID-19 at any point during their stay, whether presenting with COVID symptoms or those that were incidentally positive without symptoms. The cohort spanned a period of 16 weeks based on admission date. Patients that were not able to respond to a nursing COVID questionnaire (e.g., intubated on arrival) were excluded from this study.

Demographics and data collection

We collected a range of demographic data for each patient, including age, race, sex, smoking status, length of stay, reason for admission, ICU (intensive care unit) admission, intubation, and death. Patient comorbidities were also collected. Orthopedic manifestations were collected and categorized into myalgia, joint pain, back pain, and general fatigue/weakness. Chart review was performed by four individuals reviewing emergency department physician notes, hospital admission notes, and discharge summaries. Obesity was noted for any patient whose body mass index (BMI) was greater than 30. Patients were classified with heart disease if they had congestive heart failure, cardiomyopathies, or a history of coronary artery disease.

Statistical analysis

Statistical analyses and data processing were performed using SAS/STAT version 14.3 (SAS Institute, Cary, North Carolina, USA) to determine the association between various comorbidities, ICU stay, mortality, and the orthopedic manifestations of COVID-19 patients. The frequencies of cohort demographics and descriptive statistics were calculated and analyzed using Pearson's chi squared test, the likelihood ratio, and the NPAR1WAY procedure (ANOVA) as appropriate. The critical value for significance was set at <0.05 for all statistical tests.

Results

Of the 685 patients that tested positive for COVID-19, 185 patients presented with at least one orthopedic manifestation (27.1%). Table 1 shows the demographics for our patient cohort. Patients that experienced orthopedic manifestations were significantly younger at 53.7 years of age *versus* 58.1 years of age ($p = 0.003$) while having a significantly higher BMI at 32.6 *versus* 30.0 ($p = 0.022$). There was no significant correlation between orthopedic manifestation and race, sex, length of stay, ICU admission, death, or smoking status.

Of these 685 positive tests, 457 patients presented with COVID-19 related symptoms. The rate of new onset orthopedic manifestations among patients presenting with COVID-19 symptoms was higher at 32.4% (148 patients). In total, 259 (37%) patients were 65 years of age and older, 370 patients were male, 244 (35.6%) patients had been diagnosed with diabetes, 385 (56.1%) had been diagnosed with hypertension, 212 (30.9%) had a BMI of 30 or greater, and 185

Table 1: Demographics of all admitted COVID-19 patients.

Population Demographics			
N = 685	Ortho Manifest (−) (n = 500)	Ortho Manifest (+) (n = 185)	p-Value
Sex	M = 272 (54%) F = 228 (46%)	M = 98 (53%) F = 87 (47%)	0.78
Race	Black/AA = 272 (55%) White = 194 (39.3) Hispanic = 28 (5.7%)	Black/AA = 113 (62.7%) White = 55 (30.5%) Hispanic = 12 (6.7%)	0.12
Age*	Average = 58.1	Average = 53.7	0.006
BMI*	Average = 30.0	Average = 32.6	0.022

AA, African American; BMI, body mass index; (*) indicates statistical significance.

Table 2: Orthopedic manifestations of COVID-19-positive patients by comorbidity.

Orthopedic Manifestations Based on Comorbidity, n (%)			
Comorbidities	Population Size (N = 685)	Exhibited Orthopedic Manifestations	p-value
Hypertension			
No HTN	300	81 (27%)	0.73
HTN	385	104 (27%)	
Obesity*			
BMI <30	473	104 (22%)	0.001
BMI ≥30	212	81 (38.21%)	
Type II Diabetes*			
No Diabetes	441	107 (24.26%)	0.029
Diabetes	244	78 (31.98%)	
Heart Disease*			
None	500	147 (29%)	0.020
CHF/CAD	185	38 (20.54%)	
COPD*			
None	620	176 (28.39%)	0.012
COPD	65	9 (13.85%)	
Smoking			
History of Smoking	276	68 (24.6%)	0.61
No History of Smoking	349	98 (28.1%)	

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HTN, hypertension; (*) indicates statistical significance.

(27%) patients had been diagnosed with coronary artery disease. In total, 104 (15.2%) patients had been diagnosed with chronic obstructive pulmonary disease (COPD) and/or asthma.

Table 2 shows the prevalence of orthopedic manifestations in COVID-19 patients stratified by comorbidities. Obesity, type 2 diabetes, heart disease, and COPD/asthma comorbidities all showed a significant correlation with the musculoskeletal symptoms of COVID-19. Of the COVID-19 patients whose BMI was less than 30, 22% experienced orthopedic manifestations compared to 38.21% of those whose BMI was equal or greater than 30 ($p < 0.0001$). Overall, 31.98% of the patients that had type 2 diabetes experienced orthopedic symptoms compared to only 24.26% of patients in the non-diabetic population ($p = 0.03$). We also found that 20% of patients with heart disease experienced orthopedic manifestations compared to 29% of those without heart disease ($p = 0.02$). Finally, 28.39% of patients with no COPD/asthma had orthopedic manifestations

Table 3: Odds ratio by comorbidity for risk factors.

Odds Ratio Based on Comorbidity				
Odds Ratio	Orthopedic Manifestations			
	Yes, n (%)	No, n (%)	Odds Ratio	Confidence Interval
Obesity	81 (38.2%)	131 (61.8%)	2.19	1.54−3.12
Diabetes	78 (32%)	166 (68%)	1.47	1.04−2.07
Heart Disease	38 (20.5%)	147 (79.5%)	0.62	0.4139 0.9310
COPD	9 (13.8%)	56 (86.2%)	0.41	0.1963 0.8373

COPD, chronic obstructive pulmonary disease.

compared to 13.85% of patients with COPD/asthma ($p = 0.012$).

Table 3 shows the odds ratios for patients with obesity and diabetes (1.47 and 2.19, respectively). The odds ratios for patients with heart disease and COPD/asthma were 0.62 and 0.41 respectively.

Discussion

In the wake of the COVID-19 pandemic, concerns have been raised about the pathogenesis of the disease and its effects on various organ systems, including the musculoskeletal system. Very few studies have reported the prevalence of musculoskeletal symptoms in the COVID-19 positive population. In the study presented above, we found the overall rate of orthopedic manifestations to be 27.1% with a higher occurance in diabetic and obese patients.

As the obesity epidemic continues to grow each year, attention has been drawn to its potential effects on communicable diseases. An excessive BMI is a well acknowledged risk factor for severe symptoms in several viral illnesses including influenzas and COVID-19.[8–10] Due to a chronic state of inflammation, these patients exhibit poor antiviral responses to influenza virus infection along with an impaired ability to recover.[11] In every case, obesity has been linked to excessive respiratory and cardiac symptoms and a worse prognosis. Studies have shown that these patients have a heightened risk for acute respiratory distress syndrome, length of stay in the ICU, and the need for a ventilator. Animal studies have demonstrated that viral titers and viral spread in the respiratory epithelia are greater in obese subjects, thus leading to a worse disease burden.[12] Inflammatory markers, specifically IL-6, TNFα, and type I interferons, have been shown to have a delayed onset at the beginning of the illness but undergo significant elevations as the disease progresses when compared to subjects with a normal BMI.[13] Leptin levels have also been shown to be elevated and have a stimulative effect on inflammation in this cohort while adiponectin (anti-inflammatory adipokine) have been shown to be reduced.[14] In line with data from previous studies that investigated the compounding effect of obesity on the viral syndrome, the results of our study also suggests that there may be an excessively heightened inflammatory state when an obese patient is inoculated with COVID-19, as inferred by our findings of increased musculoskeletal inflammation in these patients. While several studies have demonstrated that obesity can exacerbate almost every cardiac or respiratory symptom of COVID-19, no studies to date have shown that musculoskeletal symptoms are also elevated in these patients.[15] In the present study, we found patients with a BMI greater than 30 presented with more musculoskeletal symptoms (38.2% *versus* 22%) and were 1.47 times more likely to experience these symptoms.

In addition to obesity, diabetes mellitus type 2 is also a well-established risk factor for viral illnesses, including COVID-19. Several studies have reported higher rates of admission to intensive care units, the use of a ventilator, and the mortality of diabetic patients; this rate can be 3.1-fold higher than non-diabetic patients infected with other respiratory viral illness outbreaks such as SARS.[6,16,17] Similarly, data published from this most recent pandemic has demonstrated that diabetic patients have far higher rates of mortality and severe illness. One study from Italy reported up to two thirds of patients that died from COVID-19 were diagnosed with diabetes.[18] Interestingly, one study that examined patients with diabetes as a singular comorbidity reported significantly higher levels of internal tissue damage in diabetic patients compared to patients with no comorbidities.[19] In addition, these authors demonstrated that diabetes may be an independent risk factors for elevated levels of IL-6, serum ferritin, erythrocyte sedimentation rate, and C-reactive protein, thus indicating a higher inflammatory state in diabetic individuals. Diabetes is an independent risk factor for the severe progression of COVID-19 due to a greater inflammatory state.[19] This was clearly demonstrated in our current patient cohort as significantly greater levels of orthopedic symptoms were seen in patients that had a diagnosis of diabetes.

Heart disease has been documented as the most common form of comorbidity among hospitalized and deceased COVID-19 patients.[20] Studies have also reported that patients with cardiac illnesses have higher levels of inflammatory markers; however, there are no studies demonstrating heart disease as an independent risk factor for elevated cytokines in these patients. Despite heart disease being a disease with a high inflammatory state,[21] our study did not reflect the higher levels of inflammation within muscular tissue as measured by patient-reported myalgias. In fact, this study showed significantly lower rates of myalgias in patients with heart disease. This may be due to the localized pathophysiology of heart disease, as it primarily affects the microvasculature of coronary vessels. Similarly, COPD has been recognized as an independent risk factor for severe pneumonia and poor outcomes. Studies have postulated that this is likely to be due to poor lung reserve and the increased expression of angiotensin converting enzyme-2 in diseased lungs.[22] Reports of COPD among COVID-19 patients in the ICU have varied tremendously.[23–25] As in the case of heart disease, COPD is a localized inflammatory condition with minimal systemic symptoms. In this study, patients with documented COPD demonstrated significantly lower rates of musculoskeletal symptoms as compared to patients without COPD.

Complaints of musculoskeletal pain have been widely reported in the literature, especially in the initial reports during the COVID-19 pandemic. One study reported that the rate of myalgias was 20.7%; however, this was a small sample size of only 174 patients in a study that was focused on patients with diabetes as the only comorbidity.[19] It is likely that musculoskeletal complaints are a result of a heightened systemic inflammatory state as demonstrated by the higher rates of myalgias in obese and diabetic patients. However, our study did not find any correlation between reported myalgias and ICU stay or overall length of stay. In addition, we suspect that the lower rates of myalgias in heart disease patients and COPD patients may be due to the relatively localized nature of these conditions and the more rapid deterioration of these patients. Based on our study and literature review, we suspect that patients with obesity and diabetes have an increased prevalence of

orthopedic manifestations of COVID-19 due to their pre-existing chronic inflammatory state.

This retrospective chart review was based primarily on physician notes and patient-reported symptoms from a single, large academic institution. Therefore, limitations exist. Patients may not have been adequately screened for musculoskeletal complaints or may have been in too poor of a condition to respond appropriately. In addition, errors in the provided documentation may have limited this study. Diversity in the patient population was limited to a single geographic location and institution. Despite these limitations, this is the first study to analyze the prevalence of orthopedic manifestations in patients positive for COVID-19, while also accounting for common comorbidities.

Orthopedic manifestations in COVID-19 are seen more often in patients with an increased BMI and diabetes mellitus type 2. Obese and diabetic patients are also at greater risk for more severe COVID-19 symptoms due to a heightened inflammatory response. Myalgias may indicate a worsening prognosis in these patients; however, more studies need to be performed to fully confirm this. Future studies may focus on the outcomes of orthopedic surgery in patients that have tested positive perioperatively and whether the common complaint of myalgias and joint pain may have further implications in this surgical cohort. Another future consideration is the long-term effects of COVID-19 on the musculoskeletal system.

Conclusion

Patients admitted with COVID-19 and a history of obesity or type 2 diabetes mellitus demonstrated significantly increased rates of orthopedic manifestations. Further investigation is now warranted to determine if myalgias are an indicator for a worsening prognosis and if there is an elevated risk for these patients, especially in the setting of orthopedic procedures and injuries. Identifying medical comorbidities and their effects on other disease states have a vital epidemiological role and could provide avenues for future therapies for at-risk populations who are diagnosed with COVID-19.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This retrospective study was approved by the University of Alabama at Birmingham Internal Review Board (Reference: 300000976; Approved 4/31/2021).

Consent

Not required.

Authors contributions

RJ, KC, JH, SP, and MS contributed to collection of data, data documenting and analysis, and manuscript preparation. SN was the senior author for this study. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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How to cite this article: Jacob R, Chandler K, Hagewood J, Prahad S, Sowers M, Naranje S. Frequency of orthopedic manifestations in COVID-19 patients. J Taibah Univ Med Sc 2022;17(2):186–191.