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Musculoskeletal Consequences of COVID-19

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Abstract: Coronavirus disease 2019 (COVID-19) is an emerging pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the majority of patients who become infected with SARS-CoV-2 are asymptomatic or have mild symptoms, some patients develop severe symptoms that can permanently detract from their quality of life. SARS-CoV-2 is closely related to SARS-CoV-1, which causes severe acute respiratory syndrome (SARS). Both viruses infect the respiratory system, and there are direct and indirect effects of this infection on multiple organ systems, including the musculoskeletal system. Epidemiological data from the SARS pandemic of 2002 to 2004 identified myalgias, muscle dysfunction, osteoporosis, and osteonecrosis as common sequelae in patients with moderate and severe forms of this disease. Early studies have indicated that there is also considerable musculoskeletal dysfunction in some patients with COVID-19, although long-term follow-up studies have not yet been conducted. The purpose of this article was to summarize the known musculoskeletal pathologies in patients with SARS or COVID-19 and to combine this with computational modeling and biochemical signaling studies to predict musculoskeletal cellular targets and long-term consequences of the SARS-CoV-2 infection.

Coronavirus disease 2019 (COVID-19) is an emerging, worldwide infectious disease pandemic that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By April 27, 2020, the virus had spread to at least 185 countries or regions and infected >3 million people, causing at least 210,000 deaths[1]. The severity of COVID-19 can be roughly categorized into 3 groups based on the severity of the initial infection[2,3]. Mild COVID-19, which, along with asymptomatic COVID-19, comprises the majority of cases, is characterized by symptoms such as fever, shortness of breath, gastrointestinal distress, malaise, headaches, and a loss of taste and smell. Patients with mild COVID-19 may or may not seek medical treatment and can sometimes present with mild pneumonia. Severely ill patients require hospitalization for treatment of the infection because of respiratory issues, and critical patients are a subset of the severely ill patients who experience respiratory failure that requires mechanical ventilation support. The percentages of patients vary, but mild cases are reported to be approximately 80%, severe cases are 14%, and critical cases are 6%[2,3]. However, as many countries prioritize testing only for hospitalized patients, determining the exact percentages of patients in the general population is challenging[4,5].

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SARS-CoV-2 belongs to the coronavirus family of positive-sense, single-stranded RNA viruses[6]. In addition to SARS-CoV-2, there are 6 other strains of coronavirus that are known to infect humans, including 4 less severe strains that cause mild symptoms, as well as the more pathogenic viruses SARS-CoV-1, which causes severe acute respiratory syndrome (SARS), and MERS-CoV, which is responsible for Middle East respiratory syndrome (MERS)[6]. There is a high degree of homology between the genetic sequences of SARS-CoV-1 and SARS-CoV-2 and extensive similarity in the predicted viral:human interactome between the 2 strains[7,8]. Both SARS-CoV-1 and SARS-CoV-2 enter cells via the angiotensin-converting enzyme 2 (ACE2) receptor using the serine protease TMPRSS2 (transmembrane protease, serine 2)[9]. Following receptor binding, proteolytic cleavage of the viral S protein by TMPRRS2 exposes a fusion peptide signal that permits mixing of viral and human membranes and release of viral RNA into the cytoplasm[10]. Once the viral RNA has access to the cytoplasm, translation of viral proteins and replication of viral RNA can occur, ultimately leading to the assembly of virions that are released from infected cells by exocytosis[10]. Several proteins encoded by viral RNA can also interact with various human cellular proteins to disrupt their function. Among the human proteins and pathways predicted to be targeted by SARS-CoV-2 proteins are those involved with intracellular vesicle trafficking, ubiquitin ligases, inflammatory signaling, nuclear transport, cytoskeletal stability, and mitochondrial respiration[7,8,11]. Therefore, the viral infection of cells can lead to the production of more virus and can severely disrupt fundamental cellular functions and lead to eventual apoptosis[7,8,11]. These apoptotic cells then contribute to tissue-level dysfunction and can also amplify local inflammation.

Studies from patients who contracted moderate and severe SARS infections have indicated a substantial musculoskeletal burden of this disease, including skeletal muscle, neurological, bone, and joint disorders[12-14]. Extended ventilator times are also known to induce proinflammatory conditions that lead to muscle and bone frailty, which can reduce overall quality of life[15,16]. In addition to directly infecting cells outside of the respiratory tract, the inflammatory response in the airway can also lead to systemic inflammation that can impact nearly every organ system, including the musculoskeletal system[17,18]. The cytokines and signaling molecules induced by the infection include C-X-C motif chemokine 10 (CXCL10), interferon gamma (IFN-γ), interleukin 1 beta (IL-1β), IL-6, IL-8, IL-17, and tumor necrosis factor alpha (TNF-α)[18,19]. Although clinical data on patients with COVID-19 following the acute care episode have been limited, there are compelling early signs of musculoskeletal dysfunction in patients recovering from COVID-19 and known musculoskeletal pathologies in patients who had SARS. Although not identical, computational biology and in vitro experimental studies have shown a high degree of similarity between the pathological response to SARS-CoV-1 and SARS-CoV-2 infection. Therefore, the purpose of this article was to summarize the known musculoskeletal sequelae of SARS and early reports for COVID-19 and analyze the epidemiological data along with molecular modeling and biochemical signaling studies to aid in the prediction of musculoskeletal targets and long-term musculoskeletal consequences of COVID-19 infection.

Identifying Potential Musculoskeletal Cellular Targets for Direct SARS-CoV-2 Infection

During the initial respiratory infection, SARS-CoV-2 is thought to predominantly infect type-II pneumocytes that line the respiratory epithelium, which express ACE2 and TMPRSS2[17]. Although the respiratory tract appears to be the primary site of infection, the compromised alveolar epithelium in some patients with COVID-19 can lead to the development of viremias[20]. Therefore, cells in other tissues may be susceptible to direct viral infection. To identify if musculoskeletal tissues express ACE2 and TMPRSS2, we performed a secondary analysis of previously published human genetic sequencing data. For skeletal muscle, cartilage, meniscus, and synovium, we used single-cell RNA sequencing (scRNAseq) data sets[21-24], which allow for the determination of gene expression in specific cell types that constitute the tissue. We could not identify scRNAseq data for human bone and instead used bulk RNA sequencing (RNA-seq) libraries of homogenized composite cortical and trabecular bone tissue and osteoblast-enriched cortical bone fractions[25]. Data from human airway epithelium[26] are shown as a control. Methods related to ACE2 and TMPRSS2 gene expression analysis can be found in the Appendix.

Within the respiratory airway epithelium, a small portion of B cells, mast cells, macrophages, type-1 and type-2 alveolar cells, and T cells express ACE2 and TMPRSS2 (Fig. 1-A). For human skeletal muscle tissue, numerous cell types express TMPRSS2, including vascular cells such as endothelial cells, smooth muscle cells, pericytes, muscle stem cells (satellite cells), macrophages, adaptive immune cells (B, T, or natural killer cells), and myonuclei (muscle fibers) (Fig. 1-A). However, only smooth muscle cells and pericytes express ACE2. Several cells in the synovium express ACE2 and TMPRSS2, including fibroblasts, monocytes, B cells, and T cells (Fig. 1-A). For articular cartilage, proliferative, hypertrophic, and effector chondrocytes (which are a subset of chondrocytes that appear to have a high level of metabolic activity) express ACE2, and only homeostatic chondrocytes (which appear to control circadian clock rhythm in cartilage) express TMPRSS2 (Fig. 1-A). In the meniscus, a small fraction of cartilage progenitors and regulatory fibrochondrocytes express ACE2, with no TMPRSS2 detected (Fig. 1-A). Whole-tissue RNAseq identified that ACE2 was expressed in nearly every sample of composite unenriched cortical and trabecular bone and in osteoblast-enriched samples (Fig. 1-B). TMPRSS2 was nearly undetectable in composite bone tissue, and TMPRSS2 was expressed in all osteoblast-enriched samples (Fig. 1-B). The bone cell marker osterix (Sp7) is shown as a control (Fig. 1-B). Human tendon and ligament transcriptional data sets were not available, but we noted an absence of ACE2 and TMPRSS2 transcript production in mouse and rat limb tendon scRNAseq and bulk RNAseq gene atlases[27,28]. Although SARS-CoV-2 has not been specifically detected in these tissues, these findings indicate skeletal muscle, synovium, and cortical bone as potential sites of direct SARS-CoV-2 infection. Cartilage could potentially be a target, but this would involve viral priming and entry in a non-cell autonomous paracrine manner. Further studies that use RNA in situ hybridization or immunohistochemistry

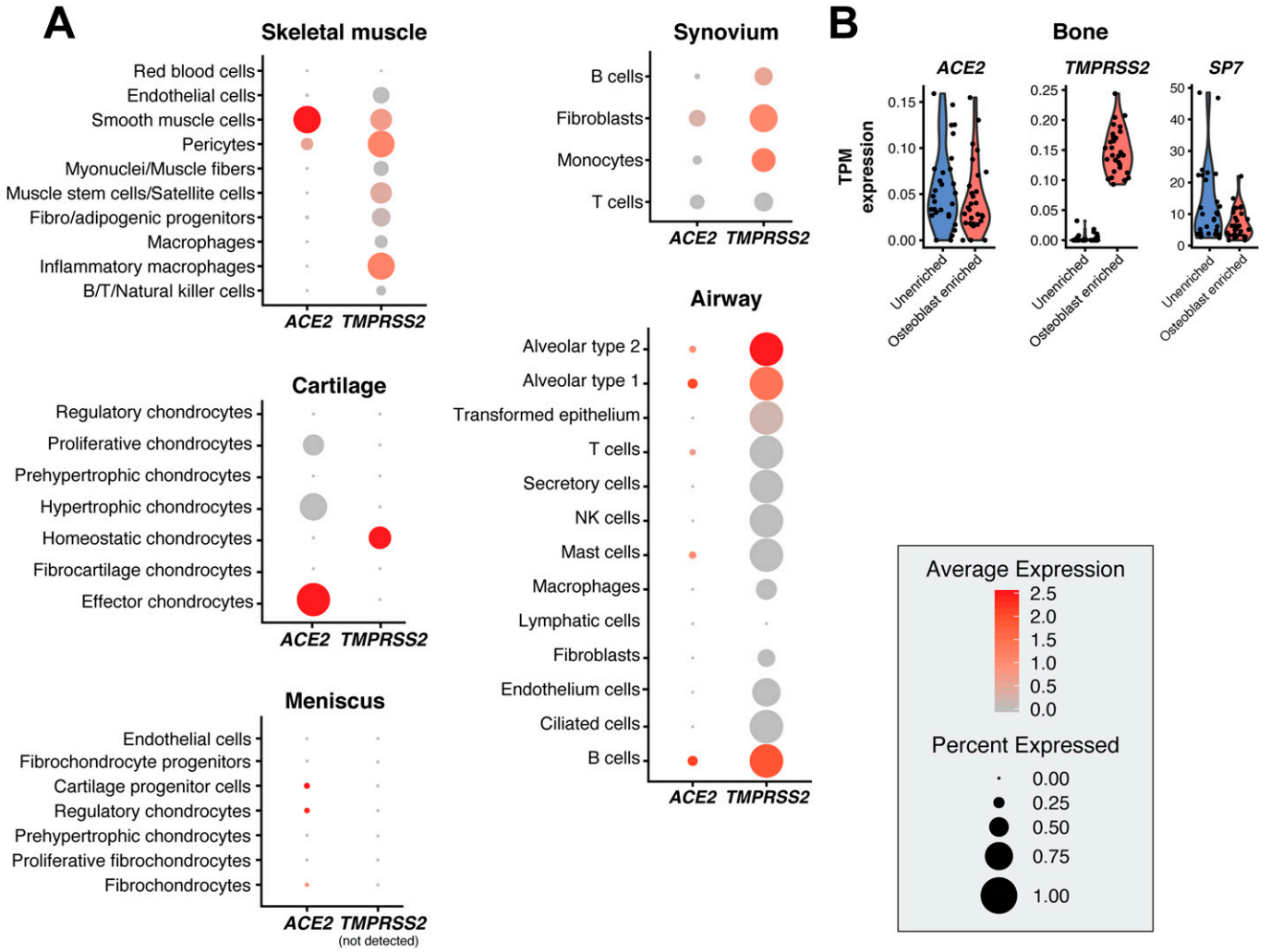

Fig. 1

Figs. 1-A and 1-B Gene expression of ACE2 and TMPRSS2 in single-cell RNA sequencing data sets (**Fig. 1-A**) and bulk RNA sequencing data sets (**Fig. 1-B**). **Fig. 1-A** The percentage of cells expressing ACE2 and TMPRSS2 and the normalized mean gene expression per cell type in the human airway, skeletal muscle, cartilage, meniscus, and synovial tissue. The percentage of expressed cells can indicate the relative presence of ACE2 and TMPRSS2-expressing cells across various tissues, although it might not capture the exact proportion of positive cells because of biases introduced by sample preparation protocols and scRNAseq technology. NK = natural killer cells. **Fig. 1-B** Gene expression of ACE2 and TMPRSS2 normalized as transcripts per kilobase million (TPM) reads from raw counts of composite cortical and trabecular bone, and osteoblast-enriched tissue fractions. Each point on the violin plot represents gene expression from a single sample, and the contour of the plot indicates the probability density of the data at different values.

using antibodies against viral proteins would clarify the presence or absence of virus in these tissues.

Skeletal Muscle

Clinical Presentation and Symptoms

Myalgias and generalized weakness have been reported to occur in one-quarter to one-half of symptomatic patients with COVID-19[29-31]. Although some data have suggested that the occurrence of muscle pain does not increase with COVID-19 severity[32], in patients with abnormal computed tomographic (CT) or radiographic imaging of the lungs, myalgias were an important predictive factor for the severity of the overall disease[33]. In a study of 214 hospitalized patients with COVID-19 in Wuhan, People's Republic of China, 19% of patients had creatine kinase (CK) levels of >200 U/L (a commonly used cutoff for clinically elevated CK), with an upper range of 12,216 U/L[34]. Loosely defined neurological symptoms that impact motor control and muscle function were reported in up to 36% of patients[34]. Extensive myalgias and muscle dysfunction have also been reported in patients with SARS[30,35-37]. The mean CK level of patients with mild and moderate SARS was 269 U/L, and it reached a mean of 609 U/L in those with a severe course of the disease[38]. Compared with age-matched healthy controls, approximately 2 to 3 months after discharge from the hospital, patients with

moderate and severe SARS had a 32% reduction in grip strength and a 13% reduction in the distance walked over a 6-minute period of time[39]. This suggests that the SARS infection leads to deficits in both muscle strength and endurance, likely due to the proinflammatory effects of the viral infection and the deconditioning that occurs during the convalescent period. The reduced functional capacity of these patients corresponded with decreases in several indices of health-related quality of life. There were occupational impacts as well, with only 40% of patients returning to work by 2 to 3 months after the acute episode of care[39,40].

Biological Mechanisms

Because of the emerging nature of COVID-19, the mechanistic effects of the infection on skeletal muscle are not fully understood. In a mouse model of SARS, within 4 days of infection, there was a rapid 20% decrease in body mass[41]. Using muscle tissue collected postmortem from patients with SARS who had died, several small studies have provided insight into the nature of muscle dysfunction as a result of SARS-CoV-1 infection[12,42,43]. Widespread muscle fiber atrophy was noted, with sporadic and focal muscle fiber necrosis and immune cell infiltration[12,42]. Electron micrographs revealed myofibril disarray and Z disc streaming[12], which would disrupt force transmission as noted in other muscle diseases[44,45]. Neuronal demyelination has also been reported in patients with SARS[42], which may also contribute to muscle weakness and fatigue.

In addition to potential direct viral infection, the cytokines and proinflammatory signaling molecules induced by the infection could lead to pathological changes in skeletal muscle tissue. C-reactive protein (CRP) is a commonly used biomarker for general inflammation, and numerous studies have demonstrated that severely ill patients with COVID-19 have CRP levels severalfold higher than healthy controls[4,46-48]. Several of the proinflammatory signaling molecules known to be elevated in patients with COVID-19[18] can also impact skeletal muscle. IFN-γ, IL-1β, IL-6, IL-17, and TNF-α can directly induce muscle fiber proteolysis and decrease protein synthesis[49-53]. Satellite cells are progenitor cells that directly contribute to muscle fiber growth, a process that is important as patients recover from COVID-19, and IL-1β and TNF-α can block the proliferation and differentiation of these cells[50,54,55]. IL-1β and IL-6 can induce muscle fibroblast activity and lead to fibrosis, which could impair muscle force production and increase injury susceptibility[56,57]. Additionally, corticosteroids were extensively used to limit acute inflammation in patients with SARS[14,58,59], and these drugs can directly induce muscle atrophy and weakness[60]. However, the U.S. Centers for Disease Control and Prevention (CDC) advises against the routine use of corticosteroids for COVID-19[61], and corticosteroid-induced muscle impairment may therefore be less of a factor in the recovery of patients with COVID-19.

Bone and Joint

Clinical Presentation and Symptoms

Less is known about bone and joint than skeletal muscle disorders in patients with COVID-19. Arthralgias are commonly reported in patients with COVID-19, but are often combined with myalgias[62-64], making it challenging to specifically identify arthralgia prevalence. Arthralgias have also been reported in patients with SARS, as well as reduced bone mineral density (BMD)[14,65]. The reduced BMD observed in patients with SARS was largely thought to be dependent on the extent and duration of treatment with corticosteroids, which were a mainstay therapy that attempted to reduce inflammation during the initial infection and subsequent early rehabilitation and recovery period[14,65]. However, decreased BMD has also been reported in other acute critical illnesses and may occur independently of treatment with corticosteroids[15,66]. Osteonecrosis has been frequently reported in patients with severe SARS, with rates from 5% to 58%[14,67]. The majority of these cases involve the femoral head, although the knee,

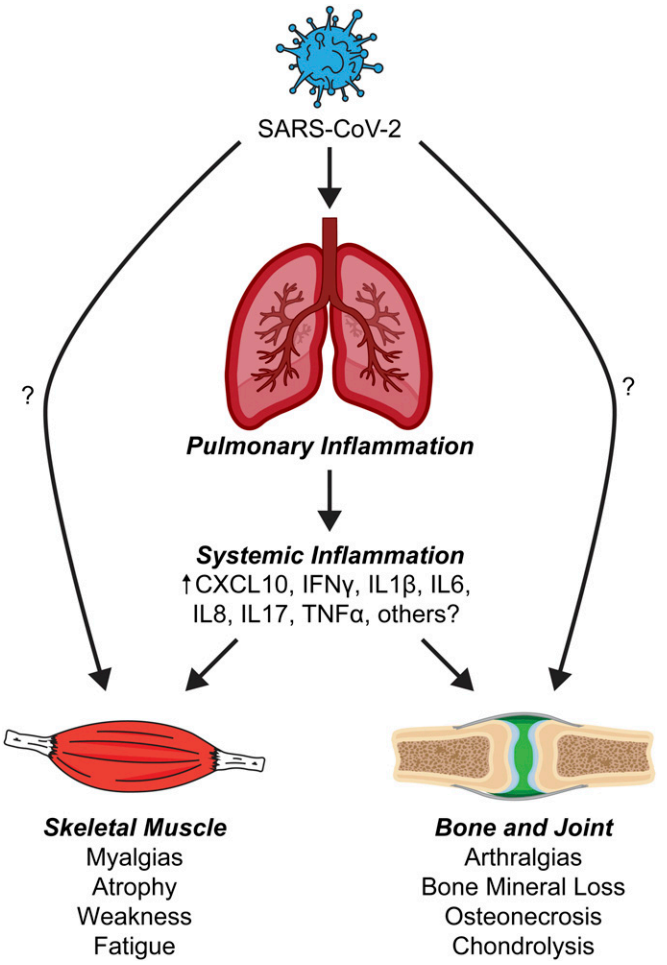

Fig. 2

Overview of indirect and potential direct effects of SARS-CoV-2 infection on musculoskeletal tissues. The primary SARS-CoV-2 respiratory infection induces systemic inflammation that can impact the musculoskeletal system. Several types of musculoskeletal cells express the ACE2 and TMPRSS2 genes, which allow for direct viral infection. However, it is unknown whether the virus can directly infect musculoskeletal tissues.

humeral head, talus, calcaneus, and other anatomical sites were affected in lower frequencies[14]. Similar to osteoporosis, patients who had higher or longer doses of corticosteroids had an elevated risk of developing osteonecrosis[14,58,68]. Hypercoagulability has also been noted in both patients with COVID-19 and those with SARS[69-71], leading to large-vessel stroke in some patients[72]. The SARS-CoV-1 infection can also induce the expression of the E3 ubiquitin ligase gene TRIM55 in vascular smooth muscle cells, which is associated with leukocyte aggregation and blood vessel inflammation[73]. The combination of hypercoagulability, leukocyte aggregation, and vessel inflammation may impair bone microvascular blood flow and contribute to the development of osteonecrosis.

Biological Mechanisms

Systemic inflammation may also play a role in bone and joint tissue physiology in patients with COVID-19. Of the cytokines known to be induced as a result of COVID-19, CXCL10, IL-17, and TNF-α have established roles in inducing osteoclastogenesis and decreasing osteoblast proliferation and differentiation, leading to a net reduction in BMD[74-76]. IL-1β, IL-6, and TNF-α can lead to chondrolysis, which could result in arthralgias or progression of osteoarthritis in some patients[77-79]. Similarly, IL-1β, IL-17, and TNF-α are thought to promote inflammation in tendinopathy and can impair the normal biological activity of tenocytes[80-82], resulting in impaired matrix remodeling and potential exacerbation of degenerative tendon disorders.

Summary

Early findings in patients with COVID-19 have identified musculoskeletal sequelae associated with this disease. Based on these reports, the epidemiological data from patients with SARS during the pandemic of 2002 to 2004, the genetic and pathological similarities between SARS-CoV-1 and SARS-CoV-2, and the frequent reporting of sarcopenia and osteoporosis in other critical illnesses[15,16,66,83], we think that it is appropriate to anticipate short-term and long-term musculoskeletal complications in patients with moderate and severe COVID-19 (Fig. 2). Conservative rehabilitation programs have been shown to improve functional recovery in patients with SARS and are effective in other critical illnesses as well[40,84]. A randomized controlled trial of 133 patients with SARS demonstrated that a 6-week progressive aerobic and resistance exercise program, consisting of 60 to 90-minute sessions that occurred 4 to 5 times per week, could be effective in improving strength and function[40]. Compared with baseline, patients who completed the program demonstrated a 10% increase in predicted VO_{2max}, a 17% improvement in grip strength, a 38% increase in shoulder flexion strength, and a 250% increase in hip extension strength[40]. The program also led to a 53% increase in curl-up repetitions per minute and a 91% increase in push-up repetitions per minute[40]. Similar rehabilitation programs, using both aerobic and resistance training to decrease fatigue and increase strength, would likely be beneficial for skeletal muscle, bone, joint, connective tissue, and cardiopulmonary health in patients with COVID-19. Because of the adverse effects of corticosteroids on skeletal muscle and bone, patients who do undergo corticosteroid treatment should be monitored for exacerbated musculoskeletal symptoms. A greater number of immunotherapies, such as IL-1 and IL-6 inhibitors, are being used off-label and in clinical trials to treat acute inflammation in patients with COVID-19[85,86], and these agents may also impact recovery of musculoskeletal function. Additionally, there are single nucleotide polymorphisms in various proinflammatory genes, such as IL-1β, IL-6, and IL-8, that can impact their biological activity and could contribute to the variation in outcomes to respiratory diseases[87]. Cohort studies focused on the musculoskeletal health of patients recovering from COVID-19 would provide important insight in identifying long-term outcomes of this devastating disease. Furthermore, outcome studies in patients with preexisting musculoskeletal diseases and those undergoing an orthopaedic surgical procedure during their illness will provide critical knowledge about mitigating the musculoskeletal consequences of COVID-19.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/F928). ■

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