What Do We Need to Know About Musculoskeletal Manifestations of COVID-19?

A Systematic Review

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Abstract

» COVID-19 is a disease that is challenging science, health-care systems, and humanity. An astonishingly wide spectrum of manifestations of multiorgan damage, including musculoskeletal, can be associated with SARS-CoV-2.

» In the acute phase of COVID-19, fatigue, myalgia, and arthralgia are the most common musculoskeletal symptoms.

» Post-COVID-19 syndrome is a group of signs and symptoms that are present for >12 weeks. The associated musculoskeletal manifestations are fatigue, arthralgia, myalgia, new-onset back pain, muscle weakness, and poor physical performance.

» Data on COVID-19 complications are growing due to large absolute numbers of cases and survivors in these 2 years of the pandemic. Additional musculoskeletal manifestations encountered are falls by the elderly, increased mortality after hip fracture, reduced bone mineral density and osteoporosis, acute sarcopenia, rhabdomyolysis, Guillain-Barré syndrome, muscle denervation atrophy, fibromyalgia, rheumatological disease triggering, septic arthritis, adhesive capsulitis, myositis, critical illness myopathy, onset of latent muscular dystrophy, osteonecrosis, soft-tissue abscess, urticarial vasculitis with musculoskeletal manifestations, and necrotizing autoimmune myositis.

» A wide range of signs and symptoms involving the musculoskeletal system that affect quality of life and can result in a decrease in disability-adjusted life years. This powerful and unpredictable disease highlights the importance of multimodality imaging, continuing education, and multidisciplinary team care to support preventive measures, diagnosis, and treatment.

COVID-19, caused by infection with a new coronavirus (SARS-CoV-2), was first identified in Wuhan, People's Republic of China, in 2019. The impacts of this emerging disease, including health, social, political, and financial casualties, on humanity are immeasurable[1].

While the world still fights against this global pandemic, the scientific community continues to develop task forces to improve diagnosis, vaccination, and treatment outcomes. Even >2 years after the index case, scientists do not know the exact pathophysiological mechanisms behind the new coronavirus disease, its late sequelae, or its

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long-term manifestations[2]. As the mortality rate is estimated to be <2%, a large number of patients have now survived COVID-19, and some of them have dealt with or are dealing with late consequences of the disease[3].

Studying the emerging data on COVID-19 complications is essential to develop preventive measures and treatment strategies to decrease morbidity and mortality and improve quality of life. Although neurologic, pulmonary, kidney, vascular, and cardiac manifestations of COVID-19 have been extensively described in the literature, musculoskeletal involvement following infection has only recently gained the due attention of the scientific community. In this study, we performed a systematic review of the literature to clarify the musculoskeletal manifestations of COVID-19.

Materials and Methods

An electronic search of PubMed/MEDLINE and Google Scholar databases from the beginning of the pandemic through January 15, 2022, was carried out. The terms for the database search included "COVID-19 AND musculoskeletal," "Coronavirus AND musculoskeletal," and "Sars-Cov-2 AND musculoskeletal." The search identified 1,521 potentially eligible studies, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 diagram[4] in Figure 1.

The inclusion criteria were scientific articles written in English that showed possible musculoskeletal manifestations in patients affected by COVID-19. Studies not addressing musculoskeletal manifestations of COVID-19 or in a language other than English were excluded. Considering that COVID-19 is an emerging and recently described disease, studies with all levels of evidence were included.

Critical analysis of titles, abstracts, and inclusion and exclusion criteria of all potentially eligible articles, followed by independent review of the full text of the selected articles by 2 investigators (R.E.P., I.G.N.R.), led to the inclusion of 95 studies that mentioned any musculoskeletal manifestation in patients affected by COVID-19. These studies were carefully evaluated for all possible musculoskeletal manifestations reported in patients who were affected by infection with SARS-CoV-2.

Results are given as absolute numbers and percentages. (Due to rounding, percentages based on the numbers do not necessarily sum to 100%.)

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No external funding was received for this study.

Results

The literature shows a wide range of extrapulmonary manifestations of COVID-19.

Of the 7 systematic reviews that were identified[5-11], 3 focused on general clinical aspects of the disease and on the more recently described "long COVID," mentioning musculoskeletal symptoms as important and frequent symptoms of the patients[5,10,11]. One review focused only on rheumatological repercussions of COVID-197. Two

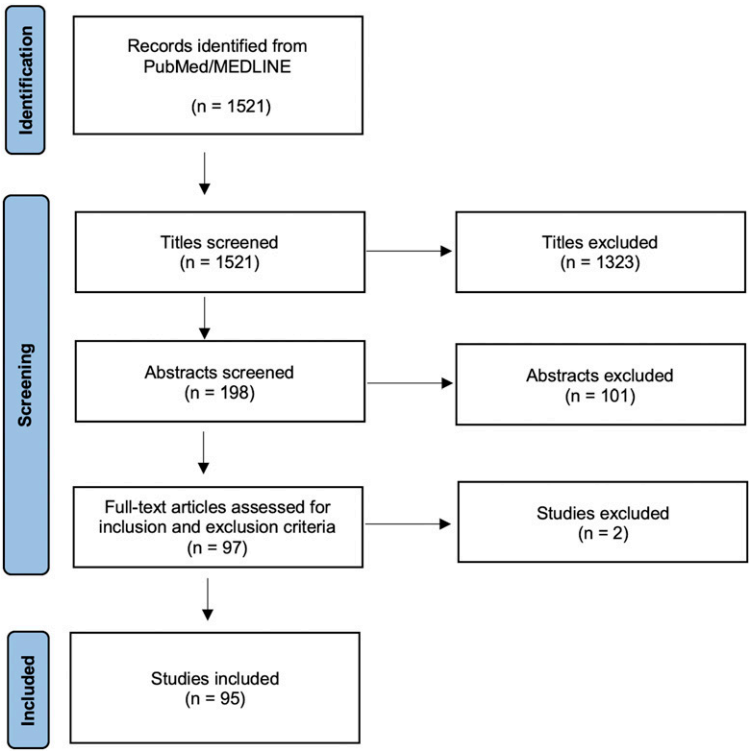

Fig. 1
PRISMA 2020 flow diagram.

reviews evaluated neuromuscular aspects of the disease[6,8]. The final systematic review investigated the increased risk of falls by the elderly following infection with SARS-CoV-29.

Twenty literature reviews were identified2,[12-30]. Of the remaining studies, 31 presented original research[31-61], 6 were case series[62-67], 24 were case reports[68-91], 1 provided a specialist's opinion[92], 4 were editorials[93-96], and 2 were letters to the editor[97,98].

Appendix 1 summarizes all musculoskeletal manifestations of COVID-19, and Figure 2 depicts the involvement of multiple systems in COVID-19.

Post-COVID-19 Syndrome

This recently described entity, also termed "long COVID," occurs in approximately 10% of survivors of COVID-19, and the rate may be higher in survivors of a severe infection[16]. Among patients with this syndrome, 77.3% reported musculoskeletal manifestations[39]. A case series stratified the manifestations into arthralgia (in 65% of those with long COVID), back pain (55%), weakness (46%), myalgia (42%), body pain (40%), fatigue (34%), and sarcopenia (28%)[64]. However, the frequency of symptoms varied across studies, with fatigue being present in up to 98% and arthralgia in up to 78;[16].

Effect of COVID-19 on Bones and Fractures

An increased risk of falls, an increased 30-day mortality after hip fracture (35.3% versus 0.9% in 1 study[31] and 15% versus 2% in another[34]), a higher prevalence of sequelae in older patients with a lower-limb fracture, reduced bone mineral density, osteoporosis, osteonecrosis, and heterotopic ossification are the currently recognized effects of SARS-CoV-2 on bone health[9,12,18,25,31,34,42,43,51,79,88,96,98]. Heterotopic ossifications were present in 10 of 52 patients with severe COVID-19, with the shoulder, elbow, and hip being the affected locations[98]. This condition

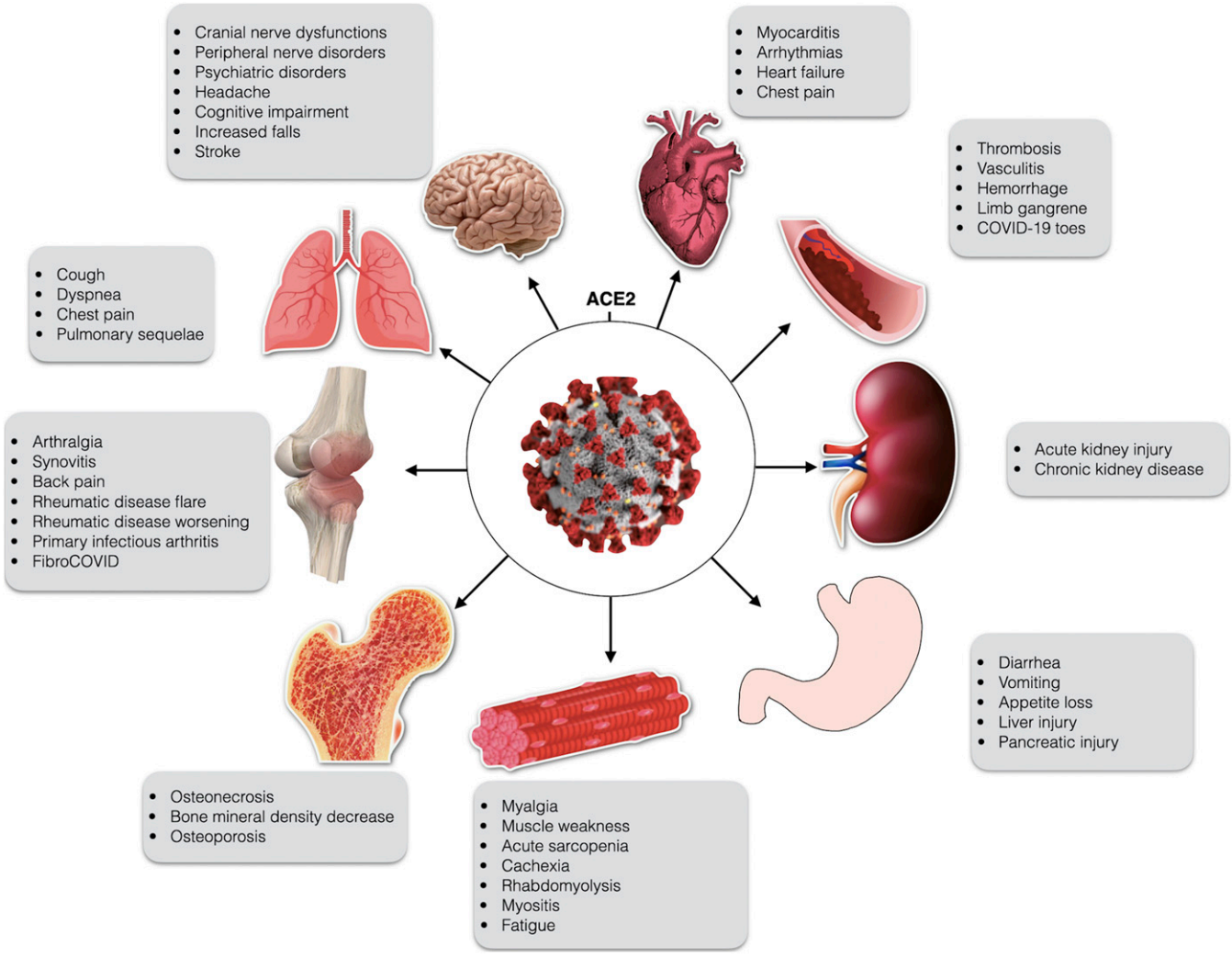

Fig. 2

The possible multisystem manifestations of COVID-19. ACE2 = angiotensin-converting enzyme 2 receptor.

was associated with longer mechanical ventilation (odds ratio [OR], 2.64; 95% confidence interval [CI], 1.26 to 5.51) and longer hospital stay (OR, 2.1; 95% CI, 1.3 to 3.4)[98]. All patients were critically ill, and most patients with heterotopic ossification were male[98].

Effect of COVID-19 on Muscles and Neuromuscular Function

Fatigue and myalgia were among the most common acute manifestations in patients hospitalized with COVID-19, being present in 38% and 15% to 44%, respectively[15]. More than 90% of the patients reported chronic fatigue, which lasted for an average of approximately 65 days after diagnosis and was more common in women and patients with a psychiatric diagnosis[2]. Myalgia, when present in combination with abnormal pulmonary imaging, was identified as a predictor of severity of the disease[12]. New-onset back pain was also a symptom, occurring in 6.8% of patients with no history of back pain[35].

Muscle weakness was a frequent finding, with an average 32% decrease in grip strength[90]. Lower inspiratory and expiratory strength was reported in 49.1% and 22.8% of patients, respectively, and 18.4% of patients with post-COVID-19 syndrome who had initially been admitted to the intensive care unit (ICU) reported muscle weakness 3 months after disease[2,21].

Rhabdomyolysis was present in approximately 14.5% of the severe cases[5,32]. Retrospective studies showed a mortality rate of 13.8% and a statistical association between increased creatine kinase levels and myalgia in patients with COVID-19[5,32,47,59].

We also found case reports or case series of critical illness myopathy, onset of Emery-Dreifuss syndrome that had been latent, Elsberg syndrome, IgG (immunoglobulin G)-related autoimmune inflammatory necrotizing myositis, and spontaneous iliopsoas hematomas[67,68,74,81,84,85]. Additional identified manifestations were acute sarcopenia, Guillain-Barré syndrome, muscle denervation atrophy, and myositis[5,8,18,22,23,52,72,92,93].

Effect of COVID-19 on Rheumatological Diseases

We found case reports and series associating COVID-19 with various rheumatological conditions such as seronegative rheumatoid arthritis, psoriatic arthritis, dermatomyositis-lupus overlap syndrome, axial spondyloarthritis, peripheral spondyloarthritis, and reactive arthritis[71,77,82,83,87]. There are also newly described conditions that seem to have a rheumatological background: sacral/buttock retiform purpura and pernio-like/"COVID-19 toes."[75,89] Fibromyalgia and urticarial vasculitis with musculoskeletal manifestations are also mentioned in the literature[17,41].

Effect of COVID-19 on Joints

In addition to rheumatological manifestations in the joints, arthralgia is also prevalent, occurring in 10% to 15% of patients[14]. When present, arthralgia is associated with increased analgesic intake and higher pain levels[25]. Other possible manifestations that were identified in the literature were adhesive capsulitis, costochondritis in children, and synovitis, presented in case reports and a letter to the editor[62,91,97].

Effect of COVID-19 on Musculoskeletal Infection

Some authors have suspected an increased risk of musculoskeletal infection after COVID-19. Case reports, case series, and a letter to the editor present many examples of orthopaedic infections in patients infected with SARS-CoV-2. A 28-year-old patient who had been discharged after a hospital admission due to COVID-19 was subsequently diagnosed with bilateral shoulder septic arthritis[80]. Primary meningococcal arthritis was also diagnosed, on the basis of a knee synovial fluid culture, in an 18-year-old man after full recovery from COVID-19[86]. Primary spinal epidural abscesses were diagnosed in a group of 6 patients with COVID-19; on admission, 3 were quadriparetic, 2 were paraparetic, and 1 was paraplegic[66]. These patients had worsening neurological symptoms, and magnetic resonance imaging (MRI) indicated diagnoses of cervical (3), thoracic (2), and lumbar (1) abscesses[66]. All patients underwent surgical treatment, and all cultures identified *Staphylococcus aureus,* with no evidence of a possible primary cause[66]. A letter to the editor from Mumbai, India, reported on musculoskeletal infections in patients with a COVID-19 history, which included an acute primary joint infection (2), soft-tissue abscess (4), and postoperative infection (6)[97].

Discussion

The spectrum of clinical presentation of patients infected with SARS-CoV-2 may vary from asymptomatic to a fatal outcome, and several studies have attempted to elucidate the factors associated with a worse prognosis[11,15]. In initial stages, the virus targets cells in the respiratory tract by binding to the angiotensin-converting enzyme 2 receptor (ACE2 receptor), which triggers the inflammatory response characteristic of COVID-19. It is important to highlight that this receptor is also present in other tissues, including muscle cells[15]. The inflammatory response is extremely complex and generates not only acute but also chronic pulmonary and extrapulmonary symptoms[99]. The complex host-pathogen interaction involves direct viral toxicity (viral replication causing multi-organ injury), endothelial cell damage (predisposing to arterial and venous thrombosis), an uncontrolled immune response (leading to a cytokine storm and a proinflammatory state), and renin-angiotensin-aldosterone system dysregulation (affecting the fluid and electrolyte balance mechanism)[99,100]. In addition, the effect of a prolonged hospital stay, especially an ICU stay, on the musculoskeletal health of patients with moderate or severe infection must be considered[19,25].

Given the summarized pathophysiology, COVID-19 has a multisystemic character. We have highlighted the musculoskeletal features related to this disease, which might be the most common manifestations and, in some cases, may be associated with a poorer prognosis and higher mortality[2,12,25]. An interesting cohort study by Hoong et al. highlights the importance of musculoskeletal manifestations: it found that 25% of COVID-19 patients with musculoskeletal symptoms had fever and did not have respiratory symptoms; additionally, a higher prevalence of fever and higher C-reactive protein (CRP) levels were identified in patients with musculoskeletal symptoms[35]. Therefore, musculoskeletal symptoms are also important to consider in the diagnosis process when COVID-19 is suspected. Some musculoskeletal symptoms were initially acknowledged as part of the early stage of the disease; however, increasing data on COVID-19 are revealing more musculoskeletal entities as complications[2,18].

In the acute phase, in addition to fever and respiratory symptoms, fatigue and myalgia are among the most common manifestations in patients hospitalized with COVID-19[15]. Myalgia was identified as a predictor of severity of the disease when it occurred in combination with abnormal pulmonary imaging[12]. Arthralgia is also prevalent in patients in the acute phase of the infection, being present in up to 15% of cases[14].

A variety of symptoms have been reported in survivors, and the exact cause of such manifestations is still not clear[2,12,18,22]. Some might be caused by the SARS-CoV-2 infection and its interaction with the host, others might be related to therapeutic approaches necessary to save the critically ill patients, and still others might be due to both factors in combination[2,12,15,18,22,79]. These complications can be part of a recently described entity, post-COVID-19 syndrome, or already recognized clinical conditions for which COVID-19's role as a risk factor is yet to be confirmed[2,10,11,101].

Although there is no consensus across reviews and original research articles on the definition of post-COVID-19 syndrome, guidelines from the National Institute for Health and Care Excellence (NICE) define it as a group of signs and symptoms that are present for >12 weeks, developed during or after infection with SARS-CoV-2, and cannot be attributed to alternative diagnoses[101]. Musculoskeletal symptoms in this syndrome include fatigue, arthralgia, myalgia, new-onset back pain, muscle weakness, and poor physical performance[10,14,16,25,33,35,36,39,40,43-45,49,55-57,61,64]. Since COVID-19 is a relatively new disease, the literature lacks follow-up data to determine the natural history of post-COVID-19 syndrome and its management. However, some risk factors have been identified, such as disease severity, female sex (in 50 to 60-year-old patients), smoking or drinking history, underlying comorbid conditions (hypertension, diabetes, obesity, cardiovascular diseases), and myalgia in the beginning of the disease course[16,39,58]. In addition, other diverse musculoskeletal complications not currently included in post-COVID-19 syndrome have been increasingly reported. Showcasing the wide variety of musculoskeletal manifestations of COVID-19, a letter to the editor from Mumbai, India, communicated an interesting group of 90 patients with a recent history of COVID-19 who received an orthopaedic consultation and were diagnosed with arthralgia/myalgia (62), synovitis (14), an acute primary joint infection (2), spontaneous osteonecrosis (2), soft-tissue abscess (4), and postoperative infection (6)[97].

Gawronska and Lorkowski[9], in a systematic review, were unable to draw a conclusion regarding the relationship between COVID-19 and an increased risk of falls by the elderly. However, lower-evidence-level studies have indicated falls to be an atypical COVID-19 presentation, and it is reasonable to think that this relationship exists due to multi-organ damage by the disease and the inherent frailty and sarcopenia of elderly patients[43]. Increased early mortality in patients with proximal femoral fracture was observed in a multicenter retrospective study that compared 30-day mortality in patients with or without COVID-19[31]. Another worrying complication in the elderly population is bone mineral density reduction, which might be explained by the association of COVID-19 with multiple factors such as long hospital stay, corticosteroid use in severely ill patients, malnutrition, decreased mobility, and alteration of osteoblast and osteoclast activity by the viral infection[2,12,18,25,42]. An editorial and a commentary drew attention to sarcopenia as a major complication that may be associated with increased morbidity and mortality in the elderly, although sarcopenia can also affect young adults infected by COVID-19[92,93].

Osteonecrosis is also a concern in patients with COVID-19[12,25]. Although universally accepted as a life-saving therapy in severe cases of COVID-19, corticosteroid therapy is a known risk factor for osteonecrosis. Therefore, this relationship is a source of concern in those who have survived severe cases[12,18,25]. In addition, a report by Agarwala et al. on patients with symptomatic osteonecrosis after COVID-19 noted that patients presented sooner than the expected (average) time after corticoid exposure and with a lower cumulative corticoid dosage than the expected (average) dosage; it was hypothesized that the host-pathogen interaction in SARS-CoV-2 infection might represent an adjuvant factor capable of causing osteonecrosis in patients with post-COVID-19 syndrome[79].

Most cases of rhabdomyolysis in patients with COVID-19 have been reported in those hospitalized with a severe infection[47,59]. However, a late case occurring after discharge has been reported, in a 67-year-old woman who developed rhabdomyolysis in both lower limbs, highlighting the unclear pathophysiology underlying this complication of infection with SARS-CoV-2[78]. The diagnosis is based on clinical findings

with laboratory confirmation. Interestingly, muscle changes may be detectable on computed tomography (CT) scans[69]. Uslu reported on an unusual case of myositis diagnosed after a patient presenting with dyspnea and lower-extremity muscle weakness was found to have an elevated creatine kinase level. MRI revealed bilateral gastrocnemius edema, and polymerase chain reaction (PCR) testing was positive for SARS-CoV-2[73]. Bahouth et al. were the first to publish imaging findings consistent with neuromuscular disease, possibly Guillain-Barré syndrome, following COVID-19; abnormal features were visible on MRI scans of a 63-year-old male patient with COVID-19 in whom multiple muscle groups in the lower limbs were affected[72].

Rheumatological disease manifestations have been reported in several patients and are being investigated[71,82,83,87]. COVID-19 appears to be a great source of inspiration in the rheumatological field due to the diverse pathophysiological mechanisms and rheumatic disease flares in patients with COVID-19. Mukarram et al. presented a case series of 5 patients with seronegative inflammatory arthritis with clinical manifestations resembling rheumatoid arthritis after being treated for COVID-19[63]. Fike et al. identified an increased risk of rheumatic disease in a cohort of Latino patients with COVID-19[38]. A web-based survey identified clinical features of fibromyalgia in patients who had recovered from infection with SARS-CoV-2[41]. The abovementioned studies suggest a possible association between COVID-19 and rheumatological disease, which might be triggered by the infection in patients with risk factors. However, this hypothesis needs to be better investigated in higher-quality studies[7,22,28,29,38,63,71,82].

An interesting entity reported by McBride et al. is retiform purpura on the sacrum and buttocks, which may represent a clinical sign indicative of infection with SARS-CoV-2 and possibly even a predictor of severity[89]. This manifestation is a cutaneous thrombotic lesion with branching, non-blanching patches or plaques on the skin of the sacrum accompanied by intergluteal hyperpigmentation. Histopathological analysis revealed full-thickness epidermal necrosis and dermal vasculopathy. Another entity is "COVID-19 toes," which is characterized by pernio (chilblains)-like lesions involving painful violaceous papules or macules on the dorsal aspects of the toes[20,75]. It has been theorized to result from endothelial damage caused by infection with SARS-CoV-2, and although low temperature typically appears to be precipitating event, it can also occur without exposure to cool temperatures, unlike primary (idiopathic) pernio[20,75,102].

An increased risk of associated bacterial infections may be a complication of COVID-19. Reported cases of musculoskeletal infection in patients with a previous history of infection with SARS-CoV-2 often did not appear to have another etiology that could explain the orthopaedic infection[66,80,86]. Considering that the SARS-CoV-2 virus can infect virtually any cell in the human body, affect multiple systems, and cause an uncontrolled immune response, it is possible that COVID-19 may cause a period of immunosuppression during which patients are more prone to becoming infected by other microorganisms. However, we were unable to locate any high-quality studies on this subject.

Certain limitations of this study should be highlighted. Although we were able to identify a large number of studies on musculoskeletal manifestations of COVID-19, studies with a high level of evidence that specifically addressed musculoskeletal involvement in patients with COVID-19 are rare, impeding the ability to draw evidence-based conclusions. Moreover, we only included English-language studies; since the SARS-CoV-2 virus affected the whole world, some studies might have been left out. For example, several populous countries that were severely affected by the pandemic might have some interesting data that are not available in the English language. In addition, we noted that the number of published papers on this topic is increasing exponentially, with the majority published in 2021. Therefore, we expect that a large number of studies with prospective designs will be available in the next months and years, along with data at longer follow-up times, higher-quality evidence, and possibly data on differences among COVID-19 variants. We also recognize that important issues such as differences in intensity of the musculoskeletal symptoms among age groups (children, young adults, middle-aged, elderly), the rate of spontaneous improvement, and the best treatment options for musculoskeletal symptoms were not addressed in this review due to the lack of relevant information in the publications pertinent to the subject. Although the type and intensity of musculoskeletal manifestations could potentially differ among the SARS-CoV-2 variants, investigation of such relationships has so far been lacking. Another potential limitation lies in the fact that it is extremely difficult to establish causal links between COVID-19 and certain musculoskeletal manifestations, since multiple confounding factors are usually present in this complex scenario. Nevertheless, viral myositis and other musculoskeletal disorders have been commonly seen in patients infected with other viruses (e.g., influenza, acute hepatitis B, chikungunya, Zika, and dengue fever)[103-105].

Based on their findings about the Zika virus, Wimalasiri-Yapa et al. suggested a possible mechanism by which activation of innate and cognate immune responses induces a chronic phase of arthropathy, and this might explain similar musculoskeletal findings in many other viral infections[105].

Therefore, we recommend that physicians be familiar with the musculoskeletal findings associated with COVID-19, since early diagnosis and a proper treatment strategy can minimize complications and optimize outcomes.

Conclusions

Infection with SARS-CoV-2 is associated with a broad spectrum of musculoskeletal manifestations. This powerful and unpredictable disease highlights the importance of multimodality imaging, continuing education, and multidisciplinary team care to support preventive measures, diagnosis, and treatment.

Additional studies with a higher evidence level are necessary to identify the whole spectrum of musculoskeletal manifestations of COVID-19, as well as to improve prognostication and propose treatment strategies.

Appendix

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/JBJSREV/A842).

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