Clinical Epidemiology of Covid-19 on Musculoskeletal

Agus Hadian Rahim[1], Ronny Lesmana[2], Renata Junilla[1], Hermawan Nagar Rayid[1], Raden Andri Primadhi[1]

[1] Department of Orthopedic and Traumatology, Hasan Sadikin General Hospital, Jl. Pasteur No. 38 *Bandung*. Kel. Pasteur Kec. Sukajadi 40161, Indonesia

[2] Physiology Division, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

*Correspondence should be addressed to Agus Hadian Rahim, Email: agus.hadian@unpad.ac.id

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Agus Hadian Rahim, MD, Sp.OT(K)., M.Epid., M.HKes (First Author)

Department of Orthopedic and Traumatology, Hasan Sadikin General Hospital, Jl. Pasteur No. 38 *Bandung*. Kel. Pasteur Kec. Sukajadi 40161, Indonesia

Ronny Lesmana, MD, PhD

Physiology Division, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

Renata Junilla, MD

Department of Orthopedic and Traumatology, Hasan Sadikin General Hospital, Jl. Pasteur No. 38 *Bandung*. Kel. Pasteur Kec. Sukajadi 40161, Indonesia

Hermawan Nagar Rasyid, MD, Sp.OT(K)., MT(BME)., PhD

Department of Orthopedic and Traumatology, Hasan Sadikin General Hospital, Jl. Pasteur No. 38 *Bandung*. Kel. Pasteur Kec. Sukajadi 40161, Indonesia

Raden Andri Primadhi, MD, Sp.OT(K)

Department of Orthopedic and Traumatology, Hasan Sadikin General Hospital, Jl. Pasteur No. 38 *Bandung*. Kel. Pasteur Kec. Sukajadi 40161, Indonesia

Abstrack

COVID-19 was declared as a pandemic on 11 March 2020 by the World Health Organization (WHO), and has currently affected more than 485 million people worldwide and caused more than 6 million of deaths (as of 31 March 2022). Musculoskeletal symptoms are common in patients with COVID-19. Many studies present the clinical aspects of COVID-19, but the involvement of the musculoskeletal system has not been deeply investigated yet. This narrative review aims to highlight the current understanding of the effect of COVID-19 on the musculoskeletal system and the potential damages caused by COVID-19 on skeletal muscles. We analyzed published reports on COVID-19-associated musculoskeletal symptoms. Literature search are performed with extensive filter of PubMed, Google Scholar, and Scopus. We identified case reports, case series, cohort studies, and meta-analyses. The last search was done on 31 March 2022. COVID-19 can cause range of musculoskeletal symptoms such as myalgia, fatigue, arthralgia, and muscle weakness.

Increased LDH and anaerobic glycolysis in COVID-19 lead to an increase in lactate level in muscles, and this can cause hypoxia and ischemic muscle pain. COVID-19 patients with critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) also tend to have difficulty weaning from a ventilator due to respiratory muscle weakness. The current therapeutics used in the management of COVID-19 patients can also cause musculoskeletal effects that clinicians should be aware of. The effective rehabilitation is critical in helping patients return to pre-infection mobility and function.

Keywords: COVID-19, Musculoskeletal.

INTRODUCTION

COVID-19 was declared as a pandemic on 11 March 2020 by the World Health Organization (WHO), and has currently affected (as of 31 March 2022) more than 485 million people worldwide and caused more than 6 million of deaths. (Globally confirmed cases of COVID-19. World Health Organization; 2020. Available from: https://covid19.who.int). The COVID-19 pandemic is caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV); based on its genetic proximity, it likely originated from bat-derived coronaviruses with spread via an unknown intermediate mammal host to humans.[1, 17]

Musculoskeletal symptoms are common in patients with COVID-19 apart from other symptoms such as fever, sore throat, dry cough, and dyspnea. Muscle weakness, fatigue or myalgia are among the most commonly reported symptoms by patients with COVID-19.[1] One study reports the prevalence of myalgia may range from 21% to more than 50% of affected patients.[2] A retrospective study by Zhang et al. reports muscle ache was one of the independent predictors for worsening of symptoms and disease status in patients with COVID-19.[3] Furthermore, the effects of current therapeutics used in the treatment of COVID-19 is important to understand that may have side effects on the musculoskeletal system. Aim of the study is to evaluate the effect of COVID-19 involved to musculoskeletal system.

Current therapy for COVID-19 includes medications such as chloroquine, hydroxychloroquine, specific antivirals, and corticosteroids. Those medications are associated with toxic myopathies, arthralgias, and other various side effects. The side effect profile of these medications may overlap and can potentially mask symptoms that can present with COVID-19.[4] Consequently, it is crucial for clinicians to understand further and investigate the musculoskeletal symptoms and presentation of those infected with COVID-19.

Many studies present the clinical aspects of COVID-19, but the involvement of the musculoskeletal system has not been deeply investigated yet. This review aims to highlight the current understanding of the effect of COVID-19 on the musculoskeletal system and the potential damages caused by COVID-19 on skeletal muscles. We analyzed the relevant reports on the topics published on PubMed, Google Scholar, and

Scopus until 2022. Additionally, we performed a literature search in the same data- base for articles on drugs used to treat COVID-19 and drugs affecting muscle functions.

Literature Search

We analyzed published reports on COVID-19-associated musculoskeletal symptoms. Literature search are performed with extensive filter of PubMed, Google Scholar, and Scopus (Figure 1). We identified case reports, case series, cohort studies, and meta-analyses. Keywords used for searching the journals reference are "COVID-19 and musculoskeletal", "SARS-CoV-2 and musculoskeletal", "COVID-19 and skeletal muscle", and "COVID-19 and neuromuscular". Full-text articles were acquired from journals' websites. We analyzed clinical characteristics of patients presenting with COVID-19-related musculoskeletal system. The last search was done on 31 March 2022.

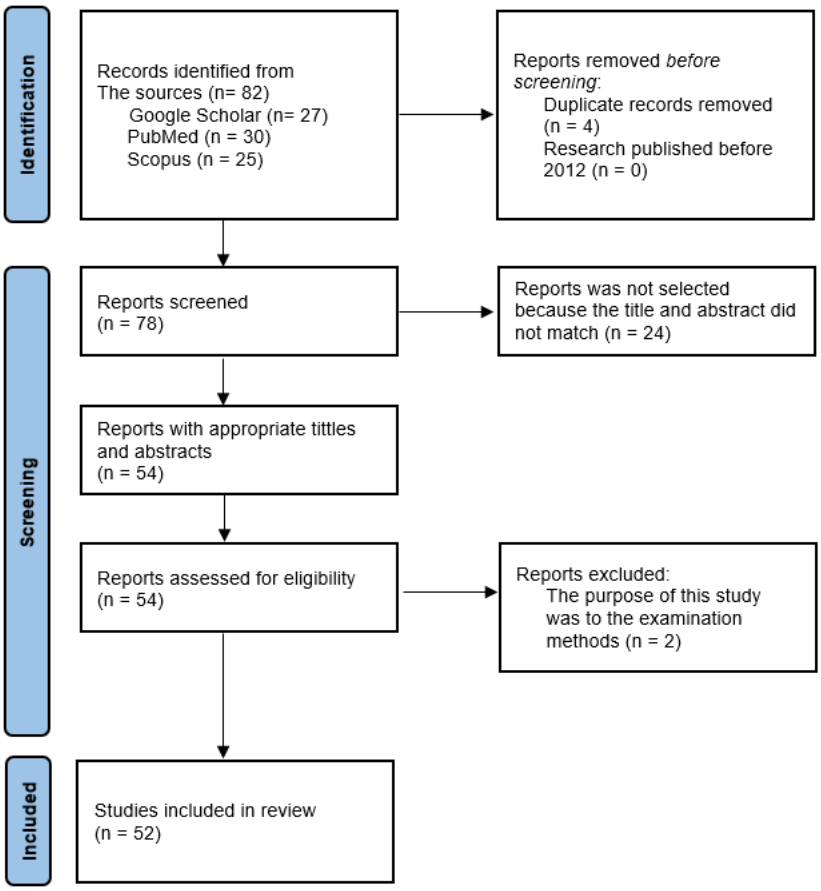

Fig. 2. Prisma Diagram

Discussion

The global pandemic caused by SARS-CoV-2, called COVID-19, has currently affected (as of 31 March 2022) more than 485 million people worldwide and caused more than 6 million of deaths. Patients with COVID-19 can vary widely in presentation, ranging from asymptomatic to severely ill and in critical condition. The severity of COVID-19 was roughly categorized into 3 groups based on the severity of the initial infection. Mild COVID-19, which is 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.[1,3,8,9] 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 who experience respiratory failure that requires mechanical ventilation support.[24] The percentages of patients vary, but mild cases are reported to be approximately 80%, severe cases are 14%, and critical cases are 6%.[9,11]

Myalgia is the common symptom of COVID-19 after fever, cough, and sore throat. Duration of myalgia may be related to the severity of COVID-19 disease.[13,14,15,36] Few patients had muscle weakness and elevated creatine kinase along with elevated levels of acute-phase reactants.[10] Muscle involvement has also been reported as evidenced by creatine kinase (CK) elevations and reports of myalgia.[13,14] While rosa et al. provide evidence that hyperckemia is associated with respiratory failure and fatal outcome. Manifestations of the muscle are not associated with the raise of CK levels; however, because of the extreme hospital circumstances, they can be easily misdiagnosed. In patients with COVID-19 infection, among other testing, CK dosage is recommended.[13,30,31] Neurological manifestations have been described in COVID-19 patients, involving the central nervous system, peripheral nervous system, and skeletal muscles.[10,14,24,31,48,49] COVID-19 patients with critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) also tend to have difficulty weaning from a ventilator due to respiratory muscle weakness. COVID19-related CIM studies have also highlighted symptoms of severe hypotrophy of the shoulder girdle and/or peroneal district. Many studies have found that ICUAW is associated with lower physical functioning at 6 months after discharge from the ICU and higher rates of mortality after discharge from the hospital at 6-months and 1-year post-ICU.[4,19,20,21,23] Tuzun et al. value handgrip strength of COVID-19 patients and found that there is muscle weakness in all patients, the loss of muscle function is related to the disease activity, especially in women. Muscle involvement in COVID-19 seems to be related to hypoxia leading to ischemic myalgia and physical fatigue.[12,26,41] Viral arthralgia is less commonly seen than myalgia in COVID-19, but has also been described in other coronavirus infections. Its low prevalence of 2% among patients infected with COVID-19 in the study is similar to that observed in other forms of viral arthralgia.[33] A Meta-analysis showed that the prevalence of neurological and musculoskeletal manifestations of COVID-19 was smell impairment (35%), taste impairment (33%), myalgia (19%), headache (12%), back pain (10%), acute cerebrovascular disease (3%), and impaired consciousness (2%). The Results showed more neurological symptoms than musculoskeletal symptoms in patients with COVID-19. This may not be surprising, as the virus is believed to be neurotrophic, and the patients may therefore present with neurological symptoms or complications, especially in long term. Similarly, it is also possible that the patients will present with more musculoskeletal symptoms and complications in the long-term due to prolonged immobilization.[31]

The effects of the SARS-CoV-2 infection on skeletal muscle are not fully understood. During the initial respiratory infection, SARS-CoV-2 is thought to predominantly infect type-II pneumocytes (express ACE2 and TMPRSS217) that line the respiratory epithelium. 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.[27,45] Therefore, cells in other tissues may be susceptible to direct viral infection.

Skeletal muscle tissue and numerous cell types of human 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 myo-nuclei (muscle fibers). Several cells in the synovium express ACE2 and TMPRSS2, that including fibroblasts, monocytes, B cells, and T cells. For articular cartilage, proliferative, hypertrophic, and effector chondrocytes (a subset of chondrocytes that appear to have a high level of metabolic activity) express ACE2, and only homeostatic chondrocytes (which control the circadian clock rhythm in cartilage) express TMPRSS2. In the meniscus, a small fraction of cartilage progenitors and regulatory fibro-chondrocytes expressed ACE2. TMPRSS2 was almost undetectable in composite bone tissue, and TMPRSS2 was expressed in all osteoblast-enriched samples. SARSCoV-2 has not been specifically detected in these tissues, these findings indicate that skeletal muscle, synovium, and cortical bone as potential sites of direct SARS-CoV-2 infection.[5,37,45] Cartilage could potentially be a target, but this would involve viral priming and entry in a non-cell autonomous paracrine manner.[15] The terms "muscle damage" and "muscle injury" have been widely used to explain muscle involvement in COVID-19 patients although there is insufficient information to support this statement. The COVID-19 can cause musculoskeletal symptoms with completely different mechanisms rather than other viral infections. Increased LDH and anaerobic glycolysis lead to an increase in lactate level in muscles, and this can cause hypoxia and ischemic muscle pain.[5,51] That is why, as the virus load decreases, the oxygenation of erythrocytes increases, muscle lactate levels decrease, and pain is relieved. The increased expression of endothelial cell adhesion molecules, which is related to coagulopathy in COVID-19 patients, causes hypoxia and is expressed by increased D-dimer levels. It can be said that patients with COVID-19 clinically present ischemic myalgia.[12]

Drug-induced myopathy is an acute or subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine kinase (CK) elevation, or myoglobinuria in patients with no pre-existing muscle diseases when exposed to certain classes of drugs.[6,16,46] Drugs can cause muscle tissue toxicity through different mechanisms. For instance by directly affecting muscle organelles (such as mitochondria, lysosomes, or myofibrillar proteins), by triggering immunologic or by inflammatory reactions; or by disrupting the electrolyte or nutritional balance, then compromising the muscle physiologic functions.[6,7,16,40] Some of drugs have been used to treat patients with COVID-19 that associate with toxic myopathy include chloroquine, hydroxychloroquine, certain antivirals, and corticosteroids.[6,16,46] The current safety profile of remdesivir, one of the anti-virals mainly used to treat COVID-19 worldwide, is still incomplete and, to date, has shown no adverse reactions on muscles.[7] The use of IFN-β and IFN-α as therapy for COVID-19 may be associated with arthralgia and myalgia in patients.[16,46] It has been reported that in patients being treated with ribavirin, >10% of patients reported arthralgia and musculoskeletal pain. Care should be given with opioid use, associated with higher in-hospital mortality, whereas other pain medications did not show a significant association with in-hospital mortality. Prolonged corticosteroid use has been associated with various effects on bone and muscle, including associations with osteonecrosis, reduced bone mineral density, osteoporosis, muscle atrophy, and muscle weakness.[4,40,46,47]

Musculoskeletal symptoms may continue to persist following recovery from COVID-19, with the most common complaints including fatigue, back pain, arthralgia, and myalgia. These symptoms can interfere with patients' ability to carry out activities of daily living (ADL). Rehabilitation may improve persistent musculoskeletal symptom, including exercise training programs and/or physical therapy. The prevention of prolonged physical inactivity can assist in minimizing muscle atrophy and loss in functional performance.[4,25,31]

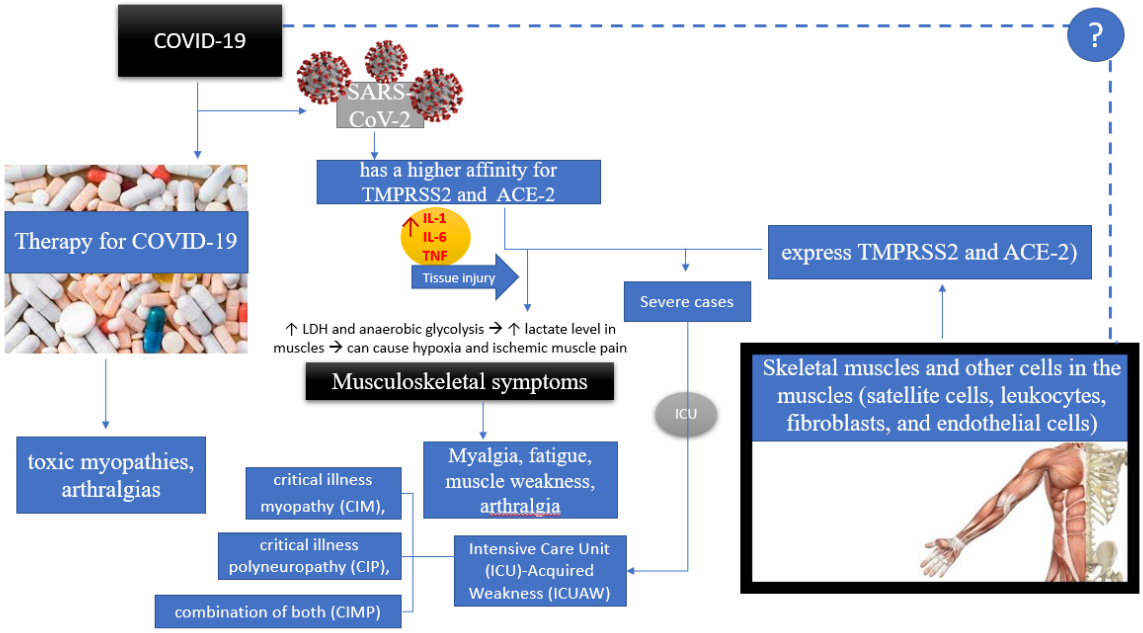

Fig. 2. Schematic Diagram of Covid-19 on Musculoskeletal

Conclusion

Taken together, the Covid-19 pandemic, musculoskeletal symptoms are quite common in patients with Covid-19. This Infection can cause range of musculoskeletal symptoms such as myalgia, fatigue, arthralgia, and muscle weakness. COVID-19 patients with critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) also tend to have difficulty weaning from a ventilator due to respiratory muscle weakness. The current therapeutics used in the management of COVID-19 patients can also cause musculoskeletal effects that clinicians should be aware of. The effective rehabilitation is critical in helping patients return to pre-infection mobility and function. The proposed schematic mechanism is presented in Figure 2.

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