

Systematic Review

Foot and ankle COVID-19 clinical manifestation: an integrative review

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Abstract

Objective: Review the literature to obtain evidence of whether COVID-19 causes or exacerbates signs and symptoms in the foot and ankle.

Methods: This is an integrative literature review. Articles from the Scielo and PubMed platforms, published between January 2020 and April 2023, were selected and obtained by combining the descriptors “COVID-19”, “Signs and Symptoms”, “Joints”, “Foot”, and “Ankle”, which answered the question guide: “What are the signs and symptoms in feet and ankles presented by patients affected by COVID-19?”

Results: Twenty-one articles were included, and data related to COVID-19 manifestation in the feet and ankles were extracted. The findings were grouped into dermatological, neurological, vascular, and musculoskeletal manifestations. The most prevalent dermatological manifestation was a chilblain-like lesion. The vascular manifestations include arterial thrombosis, vasculitis, and subacute arterial ischemia. Regarding the neurological findings, mononeuropathies and polyneuropathies were cited, including paresthesia and paresis in the feet and deep ankle areflexia. Among the musculoskeletal findings are reactive arthritis (with arthralgia in the ankle and foot, Achilles tendon enthesitis, redness, and edema), dactylitis, and heterotopic ossification in the ankle.

Conclusion: COVID-19 causes or exacerbates dermatological, neurological, vascular, and musculoskeletal signs and symptoms in the feet and ankles.

Level of Evidence IV; Diagnostic Studies; Integrative review.

Keywords: COVID-19; Signs and symptoms; Ankle; Foot; Toes.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the pandemic that emerged in late 2019 in Wuhan, China, is a determinant of a wide spectrum of systemic manifestations that define COVID-19⁽¹⁾. Respiratory signs and symptoms are the most prominent indicators of infectious pneumonia onset, ranging from mild dyspnea to severe acute respiratory syndrome (SARS). Additional extrapulmonary manifestations, including anosmia, hyposmia, ageusia, and gastrointestinal symptoms, contribute to the overall clinical manifestation. While less prevalent, these manifestations are important in defining the comprehensive

clinical profile⁽²⁾. However, although frequently reported by patients, musculoskeletal manifestations need to be better explored to corroborate the suspicion and diagnosis of the infection.

Some less reported changes have been described in the literature throughout the further investigation of the disease. Signs and symptoms in the feet and ankles are some extrapulmonary COVID-19 manifestations that should be valued for determining the correct diagnosis and properly managing COVID-19⁽³⁾.

The scarcity of publications on the symptomatology caused or aggravated by COVID-19 in the feet and ankles

Study performed at the Universidade Federal de Alfenas – UNIFAL, Alfenas, MG, Brazil.

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is remarkable. The explanation for this phenomenon is that publications focus on signs and symptoms more involved with mortality, especially the respiratory system. The objective of this study is to review the literature to obtain evidence of whether COVID-19 causes or exacerbates signs and symptoms in the foot and ankle and to corroborate the suspicion and diagnosis of such a condition in medical practice.

Methods

Our study was designed according to the necessary steps for elaborating an integrative review⁽⁴⁾. A theme was defined, the descriptors were established, the inclusion and exclusion criteria were defined, and a literature search was performed based on the descriptors. The studies were selected based on the specified criteria, and from them, the data were extracted, analyzed, and presented descriptively.

The literature search was based on the guiding question: "What are the signs and symptoms in the feet and ankles presented by patients affected by COVID-19?". The descriptors were defined based on the controlled vocabulary in the DeCS/MeSH, namely: "COVID-19", "Signs and Symptoms", "Joints", "Foot", and "Ankle". The Boolean operator used in the search was AND.

The search was conducted on the Scielo and PubMed platforms, and the inclusion criteria were publications between January 2020 and April 2023 in Portuguese, English, and Spanish, addressing signs and symptoms in the feet and/or ankles caused or exacerbated by COVID-19 and are available for full reading.

The criteria used to exclude articles were publications that did not address signs and symptoms in the feet and ankles, managed unconfirmed cases of COVID-19, addressed signs and symptoms arising from adverse effects of immunization, reported consequences of the pandemic caused by SARS-CoV-2.

The search was conducted in April 2023, resulting in 1611 studies, and 29 were selected. After a full-text read, 21 studies were included. The study followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and is summarized in Figure 1.

Data extraction was performed using a validated data collection instrument⁽⁵⁾. The article selection and data extraction were performed independently by two researchers with experience in the subject, using similar research criteria previously agreed upon, with subsequent comparison of the results; this method was performed to reduce possible interpretation biases. Articles were synthesized, and hierarchical classification was conducted regarding the level of scientific evidence, as proposed by the Agency of Healthcare Research and Quality (AHRQ).

Results

This study included 21 articles; seven were published in 2020, ten in 2021, and four in 2022. Regarding the countries

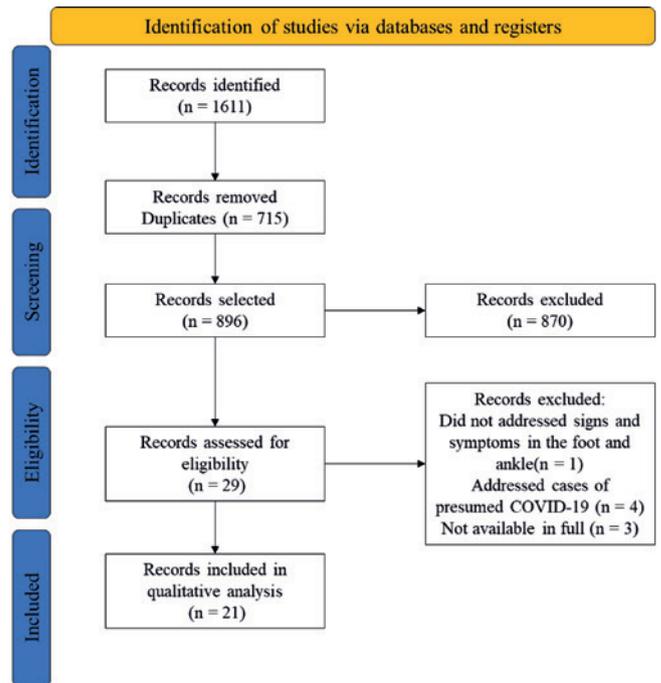


Figure 1. PRISMA flowchart, representing the search in the literature and the studies selection.

of origin of the studies, 23.80% were performed in Spain (n = 5), 19.04% in the United States of America (n = 4), 9.52% in Argentina (n = 2), 9.52% in Italy (n = 2), 4.55% in Germany (n = 1), 4.76% in Belgium (n = 1), 4.76% in Egypt (n = 1), 4.76% in Iran (n = 1), 4.76% in Japan (n = 1), 4.76% in Pakistan (n = 1), 4.76% in Portugal (n = 1), and 4.76% in the United Kingdom (n = 1). Regarding the methodologies of the publications, most articles were case reports, representing 66.66% (n = 14); the remaining were 14.28% literature reviews (n = 3), 4.76% cohort study (n = 1), 4.76% cross-sectional study (n = 1), 4.76% update article (n = 1); and 4.76% prospective study (n = 1).

The selected studies analysis showed various foot and ankle manifestations caused or exacerbated by COVID-19. Thus, the findings were grouped into four major groups according to the affected systems: dermatological, neurological, vascular, and musculoskeletal manifestations. Signs and symptoms simultaneously affected more than one system; in these cases, they were allocated to the group referring to the etiology of the manifestation or to the group in which the symptomatology was more evident in cases of etiology not completely clarified.

Dermatological manifestations were reported in nine articles, with the perniois-type lesion, also known as Covid toes, being the most cited. This manifestation has been described as a lesion with a varied appearance of erythema, papules, or macules, most often located on the toes, and may be associated with blisters, edema, pain, and pruritus. The

second most reported manifestation in the dermatological group was the necrotic lesion of the toes or soles of the feet, known as acroischemia. It was written as cyanosis, hemorrhagic blisters, and dry gangrene. Desquamation of the distal phalanges of the fingers and toes, also known as acral peeling, was another dermatological manifestation reported. Acral peeling was described as mild erythema followed by desquamation of the distal phalanges of the fingers and/or toes. Other dermatological manifestations found were acral papulo-vesicular eruption, acral urticarial lesion, acral non-inflammatory purpura and skin necrosis, acral vasculitis, acral erythema multiforme lesion, acral lesions associated with multisystem inflammatory syndrome in children and red half-moon nail sign.

Regarding peripheral neurological manifestations, three studies reported peripheral axonal mononeuropathies, two reported peripheral axonal polyneuropathies, and one reported cases of worsening pre-existing diabetic foot conditions. Among the mononeuropathies are deep knee and ankle areflexia, hypoparesis, or paresis in the knee, ankle, and foot. The manifestations of polyneuropathies were hypoparesis of ankle dorsiflexion, painless paresthesia, abnormalities in the deep knee and ankle reflexes, deep knee and ankle areflexia, abnormality of the calcaneal tendon reflex, Guillain-Barré syndrome (manifested in the ankle with hypoparesis and deep areflexia). The aggravation of the diabetic foot was evidenced by acute pain, pain at rest, and coldness sensation in the affected foot.

Regarding vascular manifestations, three studies addressed arterial thromboembolism due to COVID-19, and one study showed venous thromboembolism concomitant. The manifestations reported were discoloration of the feet, coldness sensation, claudication of small distances, subacute arterial ischemia, distal necrosis of the toes, vasculitis (Kawasaki disease), and deep vein thrombosis.

The most reported musculoskeletal manifestation in three publications was acute reactive arthritis, mainly as arthralgia that most frequently affected the metatarsophalangeal joint and ankle. In one of the cases of acute reactive arthritis after COVID-19, there was an association of Achilles tendon enthesitis. One of the publications reported dactylitis with edema and pain in the fourth and fifth toes. Another manifestation with only one report was heterotopic ossification, which affected several joints, including both ankles.

The results were compiled and presented descriptively in Table 1⁽⁶⁻²⁵⁾.

Discussion

Among the 1611 studies found, 29 were selected, and only 21 met the inclusion and exclusion criteria and were included in the qualitative analysis. A bias in selection could affect the results.

Dermatological manifestations were the most evident in the review, with the perniosis-type lesion being the

most frequently reported. Perniosis is an inflammatory vasculopathy in the toes induced by an abnormal response to cold. It can be idiopathic, hereditary, or associated with diseases such as leukemia, viral infections, and rheumatoid arthritis. The perniosis-like lesions observed in COVID-19 cases are clinically and histopathologically similar to perniosis, except for the definition of its triggering by cold⁽²⁶⁾.

A possible explanation for the perniosis-like lesions are more prevalent in young, healthy patients with mild symptoms of COVID-19 or asymptomatic patients is that these patients have an exuberant immune reaction mediated by interferon I, containing the infection early and favorably⁽²⁷⁾. The skin capillaries' lesion mechanism, which generates the lesion characteristics, involves an immune response directed to the cutaneous vessels or a direct invasion of the SARS-CoV-2 infection into the endothelium⁽²¹⁾.

Acroischemia occurs in states where SARS-CoV-2 activates the complement system in capillaries and interacts with coagulation pathways, predisposing to thrombotic microvascular damage⁽²¹⁾. This dermatological manifestation is often present in cases where innate and adaptive immunity fail to contain virus infection, resulting in a cytokine storm⁽¹¹⁾.

The involvement of the central nervous system has not yet been completely elucidated. Dos Anjos et al.⁽²⁸⁾ proposed hypotheses of direct and indirect mechanisms for neuronal involvement. Viral neuroinvasiveness was presented as a direct mechanism. Another hypothesis would be hematogenous dissemination, where infected leukocytes cross the blood-brain barrier, infecting the central nervous system. The hypothesis centered on the indirect mechanism refers to the destruction of neuron support cells, namely oligodendrocytes and astrocytes, which occur due to the cytokine storm triggered by the release of pro-inflammatory cytokines by leukocytes.

A range of neurological manifestations of COVID-19 are described in the literature; the most common are anosmia, ageusia, nausea, vomiting, headache, dizziness, confusion, and myalgia. COVID-19 is also related to the incidence of neurological diseases or complications, such as ischemic stroke, hemorrhagic stroke, cerebral venous sinus thrombosis, encephalopathy, encephalitis, oculomotor nerve paralysis, Miller-Fisher syndrome and Guillain-Barré syndrome⁽²⁹⁾.

Peripheral neuropathy is a rare neurological manifestation of SARS-CoV-2 infection, but it generates a limiting motor deficit. Oaklander et al.⁽³⁰⁾ showed that peripheral nerve involvement is related to patients with prolonged disease time and mild symptomatology. Peripheral neurological symptoms usually started one month after the COVID-19 onset and were often disabling. Finsterer et al.⁽³¹⁾ corroborates the hypothesis of immune dysregulation in peripheral neuropathy.

According to Roberts et al.⁽³²⁾ the vascular impairment of COVID-19 is hypothetically caused by the overlap of an endothelial dysfunction combined with a coagulopathy with high levels of D-dimer and fibrinogens. The mechanisms proposed to explain these phenomena vary. It includes the invasion of vascular tissue by the virus through binding to

Table 1. Results extracted from the studies included in the integrative review

Authors	Study design	Level of evidence	Sample	Comorbidities	Manifestation in the foot and ankle
Aguilar-Shea et al. ⁽⁶⁾	Case Report	5	1 participant 96 years old Male	Pulmonary bibrosis	Arterial thrombosis with 10-day evolution with pain and change of color of the right foot
Acharya et al. ⁽⁷⁾	Case Report	5	1 participant 34 years Female	SAH, sleep apnea, and morbid obesity	Neuropathy of the left sciatic nerve. Hypoparesis and hypoesthesia in the right lower limb.
Andina-Martínez et al. ⁽⁸⁾	Case Report	5	6 participants 5-13 years 4 Male 2 Female	Asthma, atopic dermatitis, and allergic rhinitis	Desquamative and erythematous acral lesions on hands and feet, which were the only manifestations of COVID-19
Brance et al. ⁽⁹⁾	Case Report	5	1 participant 54 years old Male	None	Heterotopic ossification in several joints, including the ankle, adjacent to soft tissue edema and reduced mobility
Carro et al. ⁽¹⁰⁾	Case Report	5	3 participants 50-62 years 2 Male 1 Female	Type 2 DM, SAH, obesity, dyslipidemia, pulmonary TB	Diabetic foot of atypical presentation with an extensive ischemic and infectious involvement of the feet
Dombret et al. ⁽¹¹⁾	Case Report	5	1 participant 30 years Female	None	Reactive arthritis, manifested as acute pain and erythema in the forefoot and left ankle
Farajzadeh et al. ⁽¹²⁾	Scope Review	4	Not Reported	Not reported	Acral papulo-vesicular eruption, acral urticarial lesion, acral non-inflammatory purpura, and necrosis, acroischemia associated COVID-19, acral vasculitis, chilblain-like lesion (COVID Toe), acral erythema multiform like lesion, hand and foot skin lesions associated with multisystem inflammatory syndrome in children, acral peeling conditions and red half-moon nail sign
Jimenez-Cebrian et al. ⁽³⁾	Integrative Review	3	1 systematic review 9 narrative reviews	Not reported	Perniosis-like lesion, Kawasaki disease, distal ischemia and necrosis, polyneuropathy, Guillain-Barré syndrome, isolated dermatological manifestations (desquamation, cysts, blisters, livedo reticularis and papules), recurrent herpes
Kolivras et al. ⁽¹³⁾	Prospective Study	2	32 participants 10-70 years Male and female	Not reported	Perniosis-like lesion in the feet, manifested with erythema, edema, macules, blisters, erosions, ulcers, crusts, and purples
Kopacz et al. ⁽¹⁴⁾	Case Report	5	1 participant 48 years Female	SAH, AF, antiphospholipid syndrome	Perniosis-like lesion and spasticity in the feet
Lee et al. ⁽¹⁵⁾	Cohort study	2	1 participant 74 years old Male	Psoriasis and hypoacusis	Venous and arterial thrombosis, evolving with ischemia and amputation below the left knee and right transmetatarsal
Mahmood et al. ⁽¹⁶⁾	Case Report	5	1 participant 61 years Male	SAH and type 2 DM	Lower limbs axonal mononeuropathy with reduced strength in the left ankle and no knee and plantar flexor reflexes bilaterally
Odriozola et al. ⁽¹⁷⁾	Case Report	5	4 participants 57-73 years 3 Male 1 Female	Type 1 and 2 DM but no history of diabetic neuropathy	Neuropathy with paresthesia in the feet associated with changes in sensory quantification test
Ono et al. ⁽¹⁸⁾	Case Report	5	1 participant 50 years old Male	Fatty Liver Disease	Acute reactive ankle arthritis and Achilles tendon enthesitis
Relvas et al. ⁽¹⁹⁾	Narrative Review	5	267 articles	Not reported	Perniosis-like lesion and acroischemia in the feet

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Table 1. Results extracted from the studies included in the integrative review

Authors	Study design	Level of evidence	Sample	Comorbidities	Manifestation in the foot and ankle
Rose-Salud et al. ⁽²⁰⁾	Update article	5	Not Reported	Not reported	Perniosis-like lesion and Kawasaki disease (sole edema and erythema) affecting the feet
Rubin et al. ⁽²¹⁾	Case Report	5	1 participant 27 years old Female	None	Perniosis-like lesion on toes manifested with edema, pruritus, and pain
Salvatierra et al. ⁽²²⁾	Case Report	5	1 participant 16 years Female	None	Feet dactylitis, manifested as edema in the second, fourth, and fifth toes, and associated with pain on palpation of the metatarsophalangeal joints
Taha et al. ⁽²³⁾	Cross-sectional study	3	100 participants 18–74 years 61 Male 39 Female	14 smokers, other comorbidities not reported	Reactive arthritis occurred in 37 participants, with arthralgia being the main manifestation
Tamaro et al. ⁽²⁴⁾	Case Report	5	1 participant 59 years Male	COPD, smoking	Necrotic acral lesion in left calcaneus surrounded by erythematous area
Tramonti et al. ⁽²⁵⁾	Case Report	5	1 participant 44 years old Male	Type 2 DM, obesity, and psychotic illness not specified	Axonal polyneuropathy with motor and sensory impairment, with bilateral strength deficit in ankle dorsiflexion and no deep tendon reflexes

SAH: Systemic Arterial Hypertension; DM: Diabetes Mellitus; TB: Tuberculosis; MS: Multiple Sclerosis; MIS-C: Multisystem Inflammatory Syndrome in Children; AF: Atrial Fibrillation; COPD: Chronic Obstructive Pulmonary Disease.

angiotensin-converting enzyme 2 (ACE2), cytokine storm, oxidative stress, and coagulation cascade dysfunction secondary to microcirculation dysfunction.

One of the most reported musculoskeletal manifestations in the reviewed publications was reactive arthritis, an oligoarthritis or monoarthritis that develops after one to four weeks of an infectious condition, usually urethritis or enteritis⁽¹⁰⁾. Taha et al.⁽²³⁾ demonstrated that post-COVID reactive arthritis is associated with hyperinflammation triggered by respiratory infection. This inflammation induces arthritis in post-COVID patients by its effect on the synovial membrane and articular cartilage. Inflammatory markers such as IL-6, erythrocyte sedimentation rate, and C-reactive protein measured six months after recovery are statistically associated with post-COVID arthritis.

An important limitation identified during the development of this study was the lack of comprehensive differential diagnoses for manifestations attributed to the virus infection.

While articles addressing cases of symptom emergence or exacerbation in confirmed COVID-19 cases were included, not all rigorously provided a thorough exploration of alternative explanations for these manifestations.

Conclusion

COVID-19 causes or exacerbates dermatological, vascular, neurological, and musculoskeletal manifestations in the foot and ankle. While uncommon, these manifestations may occur as primary symptoms of the disease or the worsening of pre-existing conditions. Although infrequent, recognizing such signs and symptoms corroborates the assertiveness in the suspicion of SARS-CoV-2 diagnosis, especially when the systemic and respiratory symptoms are mild and nonspecific. However, new studies presenting a higher level of scientific evidence are necessary to affirm the causality between SARS-CoV-2 infection and manifestations in the feet and ankles.

Authors' contributions: Each author contributed individually and significantly to the development of this article: VHMR *(<https://orcid.org/0000-0003-0154-7385>) conceived and planned the activities that led to the study, approved the final version; GSB *(<https://orcid.org/0000-0003-1753-2655>) wrote the article EASJ *(<https://orcid.org/0000-0002-5054-874X>) participated in the review process. All authors read and approved the final manuscript.*ORCID (Open Researcher and Contributor ID) 

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