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Systematic Review

The development of inflammatory arthritis following SARS-CoV-2 infection: a systematic review of the literature

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Background: Given the widespread impact of COVID-19, it is important to explore any atypical presentations and long-term sequelae associated with this viral infection, including the precipitation of inflammatory arthritis.

Objective: To identify and summarize clinical reports of acute inflammatory arthritis associated with COVID-19.

Methods: A systematic review of the PubMed (MEDLINE), Google Scholar, and Cochrane Central databases through January 31, 2022 was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The inclusion criteria were: human subjects and English language. Data extraction and qualitative synthesis of the demographics, clinical presentations, treatments, and outcomes were performed. Quality assessment was performed using the Joanna-Briggs Institute critical appraisal tools.

Results: A total of 37 articles collectively describing the cases of 54 patients were included. The mean age was 48.2 years (6-78 years). 53.7% of patients were male and 46.3% were female. The onset of articular symptoms varied considerably, and the majority of cases were described as polyarticular (29). The classification of inflammatory arthritis in the included studies was as follows: reactive (19), post-viral (13), new-onset rheumatoid arthritis (RA) (8), crystal-proven arthropathy flare (4), acute viral (2), new-onset psoriatic arthritis (2), flare of preexisting RA (2), and other (4). Arthritis treatment regimens varied but consisted largely of NSAIDs and corticosteroids with most patients experiencing improvement or resolution of their joint symptoms.

Conclusion: There is limited low-level evidence suggesting that patients may develop acute arthritis during or after SARS-CoV-2 infection. This review highlights the need for further research to elucidate the relationship between COVID-19 and the development of inflammatory arthritis.

Lay summary

This review paper sought to explore the relationship between COVID-19 disease and acute joint pain/inflammation (arthritis) through a systematic search of the literature. This review found limited low-level evidence suggesting that patients may develop inflammatory arthritis during or after COVID-19 disease. However, there is a need for further research to improve our understanding of the relationship between COVID-19 and the development of inflammatory arthritis.

Key words: infectious diseases, inflammatory processes/inflammatory markers, musculoskeletal/connective tissue disorders, pain, rheumatology/arthritis

Introduction

As of early 2022, over 392 million individuals have been infected with SARS-CoV-2 globally.[1] In light of the widespread impact of COVID-19, it is critically necessary to elucidate atypical presentations and long-term sequelae of this viral infection. Many viruses, including SARS-CoV-2, have been associated with rheumatological and autoimmune manifestations; these manifestations include acute inflammatory arthritis. There have been various associations between infectious processes and inflammatory arthritis described in the medical literature. Most notably, several pathogens, including *Chlamydia trachomatis*, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter*, are known to trigger reactive arthritis, which typically presents within 2 to 4 weeks of the preceding infection as an acute asymmetric oligoarthritis involving the larger joints.[2] Although more commonly associated with gastrointestinal and sexually-transmitted infections, there have been reports of reactive arthritis triggered by respiratory infections as well.[3] It is also important to note that several viruses, such as parvovirus B19, hepatitis B and C, chikungunya, and Epstein-Barr virus are associated with acute viral arthritis or post-infectious arthritis, which typically manifests as an acute onset polyarthritis.[4] Moreover, there is also considerable literature, indicating that viruses are a major trigger of autoimmunity via various immune pathways.[5,6] For example, Joo et al.[6] reported that ambient respiratory viral infections, including other coronaviruses, are associated with an increased number of incident rheumatoid arthritis (RA) cases.

Therefore, it is imperative that clinicians have an awareness of the potential association between COVID-19 infection and acute inflammatory arthritis as such clinical presentations may become more prevalent over time given the increasing number of individuals who have contracted the SARS-CoV-2 virus to date and are, therefore, susceptible to developing rheumatological and autoimmune sequelae related to their prior COVID-19 infection at some point in the future. The purpose of this study was to identify and summarize all clinical reports of acute inflammatory arthritis associated with

Key messages

- Several cases of acute arthritis during/after COVID-19 disease have been reported.
- Many of these cases were classified as reactive arthritis or post-viral arthritis.
- The included studies were low-level evidence (e.g. case reports, case series).
- Further research on the relationship between COVID-19 and acute arthritis is warranted.

SARS-CoV-2 infection published in the peer-reviewed literature through a systematic review.

Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was used in identification and selection of studies for this review.[7] Two separate comprehensive literature searches of the PubMed (MEDLINE), Google Scholar, and Cochrane Central databases from inception through January 31, 2022 were performed in February 2021 and February 2022 to identify all clinical reports of inflammatory arthritis associated with SARS-CoV-2 infection. Various combinations of the following keywords were used in the search strategy: inflammatory arthritis, post-viral arthritis, reactive arthritis, acute arthritis, COVID-19, SARS-CoV-2, and novel coronavirus; no filters or limits were used in the search. Once the database search was complete, duplicates were removed, and the titles and abstracts of the remaining articles were screened by two independent reviewers. All clinical reports of human subjects in the English language were included in this review. Review articles, animal studies, cadaveric or otherwise in vitro studies, and non-English articles were excluded. Articles that met the inclusion criteria underwent full-text review by two independent reviewers. The references of all selected studies were reviewed to minimize exclusion of relevant studies. Any discrepancies in study selection were to be reviewed by a third more senior author to obtain consensus.

Data extraction and synthesis

Data extraction was performed by two independent reviewers using a standardized Microsoft Excel spreadsheet. Clinically relevant data were extracted from the selected articles and synthesized. When available, the following data were recorded: demographics (e.g. age, sex, and race), COVID-19 infection (e.g. testing, severity, and treatment), arthritis clinical manifestations (e.g. symptom onset in relation to acute COVID-19 infection, rheumatologic localization, associated findings, and arthritis classification), comorbidities, diagnostic evaluation (e.g. imaging findings and biomarkers), treatment rendered (e.g. topical/oral medications and injections), and clinical outcomes (e.g. symptom resolution and recovery). Due to heterogeneity of the clinical data points reported in the included clinical reports and the limited number of patients, meta-analysis was not performed. Therefore, the extracted data were synthesized qualitatively, and descriptive statistics were calculated to report demographics (e.g. age and sex) and clinical findings in aggregate using Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). The data underlying this article are available within the article. A PRISMA checklist for this systematic review is available in the online supplementary material.

Quality assessment

Quality of the included studies was assessed using the Joanna-Briggs Institute (JBI) critical appraisal tools for case reports and case series.[8] However, no predetermined cut-off scores were established for inclusion of studies as it was anticipated that a limited number of eligible clinical reports would be available for review in the peer-reviewed literature at the time of this review given that SARS-CoV-2 is a relatively novel virus.

Results

Study characteristics

Two systematic searches of the PubMed (MEDLINE), Google Scholar, and Cochrane Central databases yielded a total of 680 articles; 37 of these articles met our inclusion criteria and were, therefore, included for further review.[9–45] A PRISMA flow diagram delineating our database search results and rationale for exclusion of articles is presented in Figure 1. Collectively, the 37 studies (30 case reports, 7 case series) described the cases of a total of 54 patients who developed inflammatory arthritis during acute COVID-19 infection or following COVID-19 infection. The mean JBI score for the included case reports was 6.8 (0.5) out of 8. The mean JBI score for the included case series studies was 5.4 (1.3) out of 10. Most articles originated from Italy (8) followed by Japan (4) Iran (3) and the USA (3). Details for each reported case are delineated in Table 1.

Patient demographics

The percentage of males and females were 53.7% (n = 29) and 46.3% (n = 25), respectively. The mean age for patients was 48.2 years (6-78 years); exact age was not reported for two cases.[18,34] Only 9 of the included studies explicitly stated the patient's race or ethnicity as noted in Table 1. The overwhelming majority of patients did not have a personal history of preexisting joint symptoms or autoimmune disease. Pertinent comorbidities included preexisting RA in one of the cases described by Alivernini et al.[9] as well as one of the cases described by Derksen et al.,[17] gout with recurrent acute arthritis in three of the cases described by Lopez-Gonzalez et al.,[29] gout in each of the cases described by Ouedraogo et al.[35] and Shimoyama et al.,[40] unspecified recurrent acute arthritis in one of the cases described by Lopez-Gonzalez et al.,[29] remote history of septic arthritis in one of the cases described by Sinaei et al.,[42] chronic intermittent monoarticular joint pain in the case described by Kuschner et al.,[27] sarcoidosis in one of the cases described by Derksen et al.,[17] and autoimmune hypothyroidism in two cases described by Colatutto et al..[14] A comprehensive list of the comorbidities reported for each

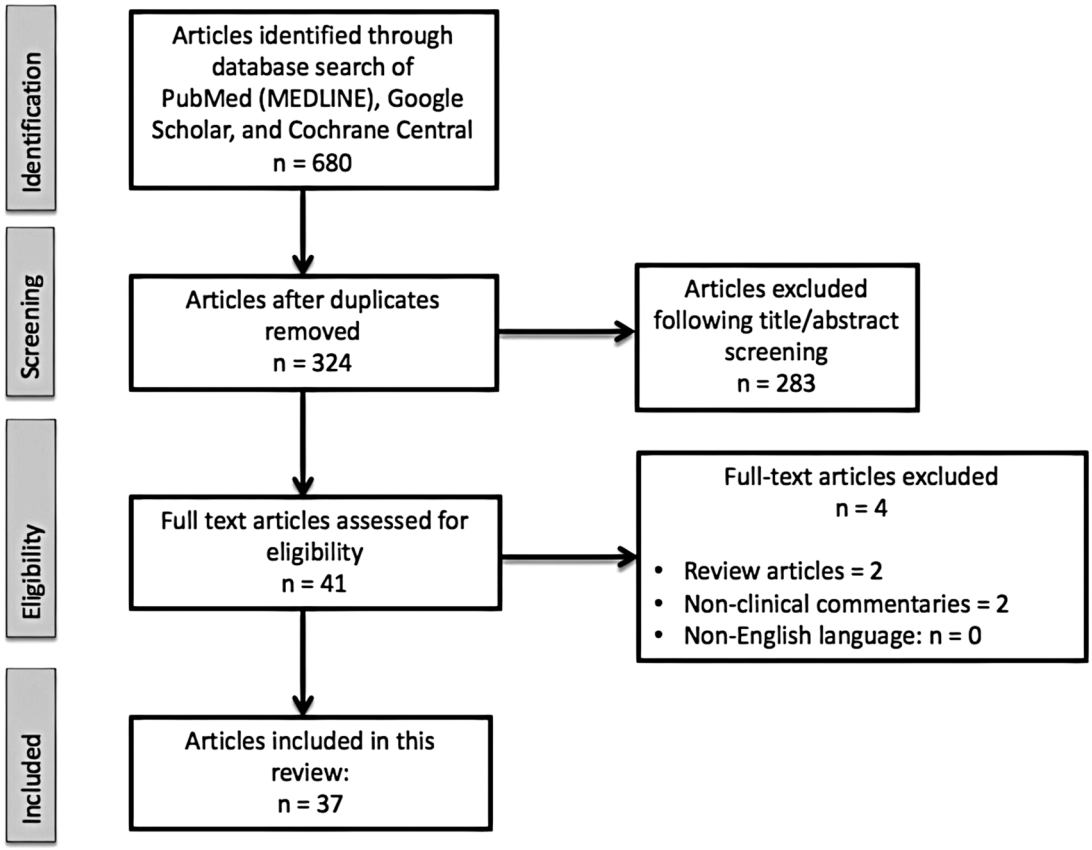

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram describing the inclusion process for studies in the systematic review.

patient can be found in Table 1. A positive family history of autoimmune disease was reported in two cases; Talarico et al.'s[44] case had a family history of ankylosing spondylitis, and Novelli et al.'s[32] case had a family history of psoriasis.

COVID-19 disease course

Patients in the included studies were confirmed to have active or prior SARS-CoV-2 infection either via real-time polymerase chain reaction (RT-PCR) or serology. In terms of disease severity, 35 cases were described as being mild or moderate, 16 cases were described as either moderate-to-severe or severe, and 3 cases did not have sufficient details to ascertain COVID-19 disease severity. Treatment for acute COVID-19 infection varied considerably with the most common pharmacological treatment being antibiotics (n = 17) followed by hydroxychloroquine (n = 13). The need for supplemental oxygen/mechanical ventilation was reported in 6 cases. The specific COVID-19 treatment regimens reported for each case are detailed in Table 1. Of note, specific details on COVID-19 treatment regimens were not reported for 24 of the included cases.

Clinical Manifestations of Acute Arthritis

The classification of acute inflammatory arthritis in the included studies was as follows: reactive (19), post-viral (13), new-onset RA (8) crystal-proven arthropathy flare (4), acute viral (2), new-onset psoriatic arthritis (2), flare of preexisting RA (2), and other (4). Figure 2 illustrates the classifications of arthritis for cases included in this review. Onset of articular symptoms ranged from 6 weeks prior to acute COVID-19 infection to 3.5 months following acute COVID-19 infection with the mean onset being approximately 4 weeks after acute COVID-19 symptom onset. The cases varied considerably in terms of rheumatologic localization with most cases being described as polyarticular (n = 29) followed by monoarticular (n = 12), oligoarticular (n = 8), axial (n = 3), and oligoarticular/axial (n = 1). One case did not provide sufficient details on rheumatologic localization.[12] There was considerable variability in terms of the joints involved as detailed in Table 2. Associated cutaneous findings were reported in six cases and included maculopapular rash, urticaria, lesions consistent with psoriasis, palpable purpura, pruritic clearly demarcated erythematous scaly patches, and leukoderma with an associated unspecified rash.[12,15,18,24,32,39] The diagnostic work-up varied across cases with most authors reporting results of one or more inflammatory markers and auto-antibody panels. However, arthrocentesis with synovial fluid analysis was only reported for 19 cases. In addition, imaging findings were reported for 35 cases with the most frequently reported findings being consistent with non-specific inflammation, including joint effusion, synovial tissue thickening, and increased vascularity. Detailed biomarker and imaging findings are outlined in Table 2.

Treatment and outcomes of acute arthritis

The majority of cases were treated with non-steroidal anti-inflammatory agents (NSAIDs) and/or systemic corticosteroids. Disease-modifying antirheumatic drugs (DMARDs),

Table 1. Patient characteristics and clinical manifestations of COVID-19 infection.

Primary author	Design (JBI score)	Country	Age sex	Race/ ethnicity	Comorbidities	COVID-19 diagnosis	COVID-19 treatment	COVID-19 severity
Alivernini[9] (patient 1)	Case series (5)	Italy	61M	NR	NR	Nasal RT-PCR	Lopinavir-Ritonavir, HCQ	Mild
Alivernini[9] (patient 2)	Case series (5)	Italy	50F	NR	RA: (+) ACPA/RF in 2017; in sustained remission on Methotrexate 15 mg/wk (held during admission)	Nasal RT-PCR	Lopinavir-Ritonavir, HCQ, Ceftriaxone, Azithromycin	Severe
Baimukhamedov[10]	Case report (7)	Kazakhstan	67 M	NR	NR	RT-PCR	Ceftriaxone, Azithromycin, Ibuprofen	Moderate
Ben-Chetrit[11]	Case report (6)	Israel	33 F	NR	NR	RT-PCR	NR	Mild infection followed by asymptomatic re-infection 5 months later
Chandrashekara[12] (patient 1)	Case series (4)	India	66M	NR	NR	NR	NR	NR
Chandrashekara[12] (patient 2)	Case series (4)	India	78M	NR	Diabetes mellitus, asthma	Serology	NR	NR
Chandrashekara[12] (Patient 3)	Case series (4)	India	31F	NR	NR	Serology	Unspecified antipyretics and antibiotics	Mild
Chandrashekara[12] (Patient 4)	Case series (4)	India	39F	NR	NR	Serology	NR	Mild
Coath[13]	Case report (7)	United Kingdom	53M	NR	Lumbar disc herniation in mid-20s with resulting radiculopathy and foot drop s/p discectomy (successful management), hyperlipidemia	Serology	NR	Mild
Colatutto[14] (Patient 1)	Case series (5)	Italy	58 F	NR	Autoimmune hypothyroidism	Nasal RT-PCR	HCQ, Azithromycin	Mild
Colatutto[14] (Patient 2)	Case series (5)	Italy	53 F	NR	Autoimmune hypothyroidism	Nasal RT-PCR	HCQ, Azithromycin	Mild
Crivelenti[15]	Case report (7)	Brazil	11 F	Brazilian	NR	Serology	Human immunoglobulin, aspirin	Severe (complicated by MIS-C)
Danssaert[16]	Case report (7)	USA	37F	NR	Congestive heart failure, asthma, GERD, morbid obesity s/p bariatric surgery	Positive unspecified test	NR	Mild
Derksen[17] (Patient 1)	Case series (5)	Netherlands	67 M	NR	NR	Positive unspecified test	NR	Moderate-to-severe
Derksen[17] (Patient 2)	Case series (5)	Netherlands	49 M	NR	NR	Positive unspecified test	Ceftriaxone	Moderate-to-severe
Derksen[17] (Patient 3)	Case series (5)	Netherlands	70 F	NR	Preexisting RA previously in remission for 5 years	Positive unspecified test	NR	Moderate-to-severe
Derksen[17] (Patient 4)	Case series (5)	Netherlands	67 F	NR	Sarcoidosis	Positive unspecified test	NR	Moderate-to-severe
Derksen[17] (Patient 5)	Case series (5)	Netherlands	65 M	NR	NR	Positive unspecified test	NR	Moderate-to-severe

Table 1. Continued

Primary author	Design (JBI score)	Country	Age sex	Race/ ethnicity	Comorbidities	COVID-19 diagnosis	COVID-19 treatment	COVID-19 severity
De Stefano[18]	Case report (6)	Italy	30sM	NR	NR	Nasal RT-PCRSerology	Supportive care	Mild
Di Carlo[19]	Case report(7)	Italy	55M	NR	NR	Nasal RT-PCR	NR	Mild
Drosos[20]	Case report (7)	Greece	46 F	NR	None	RT-PCR	Supportive care (paracetamol)	Mild
Fragata[21]	Case report (7)	Portugal	41F	NR	NR	Nasal/Oropharyngeal RT-PCRSerology	Supportive care	Mild
Gasparotto[22]	Case report (7)	Italy	60 M	Caucasian	None	Nasal RT-PCR	HCQ, Ceftriaxone, Azithromycin, anticoagulation prophylaxis, mechanical ventilation	Severe
Hønge[23]	Case report (7)	Denmark	53 M	NR	None	Oropharyngeal RT-PCR	Remdesivir, Dexamethasone, supplemental oxygen	Severe
Houshmand[24]	Case report (7)	Iran	10M	NR	NR	Nasal/Oropharyngeal RT-PCR	Acetaminophen, Cefixime, Cetirizine, Desloratadine, Hydroxyzine	Mild
Jali[25]	Case report (7)	Saudi Arabia	39F	Saudi Arabian	NR	Nasal RT-PCR	NR	Mild
Kocyigit[26]	Case report (7)	Turkey	53 F	NR	Hypertension	Nasal RT-PCR	HCQ, Favipiravir, Azithromycin, anticoagulant, supplemental oxygen	Moderate
Kuschner[27]	Case report (6)	USA	73 M	NR	Hypertension; chronic, intermittent right wrist pain	Positive unspecified test	NR	Mild
Liew[28]	Case report (7)	Singapore	47M	Indian	NR	Nasal/Oropharyngeal RT-PCR	NR	Mild
Lopez-Gonzalez[29](Patient 1)	Case series (8)	Spain	71M	NR	Gout (on Allopurinol), recurrent acute arthritis	Nasal RT-PCR	HCQ	Severe
Lopez-Gonzalez[29](Patient 2)	Case series (8)	Spain	61M	NR	Gout (on Allopurinol), recurrent acute arthritis	Nasal RT-PCR	HCQ, Azithromycin, Tocilizumab, Methylprednisolone	Severe
Lopez-Gonzalez[29](Patient 3)	Case series (8)	Spain	64M	NR	Recurrent acute arthritis (no prior work-up or treatment)	Nasal RT-PCR	HCQ, Azithromycin, Lopinavir-Ritonavir, Tocilizumab	Severe
Lopez-Gonzalez[29] (Patient 4)	Case series (8)	Spain	45M	NR	Gout (on Allopurinol; held during admission), recurrent acute arthritis	Serology	HCQ, Tocilizumab, Methylprednisolone	Severe
Mukarram[30] (Patient 1)	Case series (5)	Pakistan	65 F	NR	Hypertension	Self-reported	NR	Mild
Mukarram[30] (Patient 2)	Case series (5)	Pakistan	35 M	NR	None	Self-reported	NR	Mild

Table 1. Continued

Primary author	Design (JBI score)	Country	Age sex	Race/ ethnicity	Comorbidities	COVID-19 diagnosis	COVID-19 treatment	COVID-19 severity
Mukarram[30] (Patient 3)	Case series (5)	Pakistan	25 F	NR	None	Self-reported	NR	Mild
Mukarram[30] (Patient 4)	Case series (5)	Pakistan	32 F	NR	None	Self-reported	NR	Mild
Mukarram[30] (Patient 5)	Case series (5)	Pakistan	40 M	NR	Diabetes mellitus	Self-reported	NR	Mild
Neves[31]	Case report (7)	Portugal	28 M	NR	None	RT-PCR	Mechanical ventilation, Amoxicillin	Severe
Novelli[32]	Case report (6)	Italy	27F	NR	Irritable bowel disease (family history of psoriasis)	Serology	NR	Mild
Ohmura[33]	Case report (6)	Japan	42 F	NR	Diabetes mellitus	RT-PCR	NR	Moderate
Ono[34]	Case report (7)	Japan	50sM	NR	Steatohepatitis	Nasal RT-PCR	Favipiravir, Cefepime, Vancomycin; mechanical ventilation	Severe
Ouedraogo[35]	Case report (7)	USA	45 M	Black	Chronic low back pain post spinal fusion; isolated episode of crystalline (–) podagra 12 years prior	Nasal RT-PCR	HCQ, Tocilizumab, Ceftriaxone, Azithromycin, mechanical ventilation, ECMO, hemodialysis	Severe
Parisi[36]	Case report (7)	Italy	58F	White	NR	Nasal RT-PCR	Paracetamol	Mild
Perrot[37]	Case report (7)	France	60F	NR	None	RT-PCR	HCQ, Azithromycin, Zinc Gluconate	Mild
Saricaoglu[38]	Case report (7)	Turkey	73M	NR	Diabetes mellitus, hypertension, coronary artery disease	Nasal/Oropharyngeal RT-PCR	HCQ, Ceftriaxone, Azithromycin, Enoxaparin	Moderate
Schenker[39]	Case report (7)	Germany	65F	Caucasian	NR	Serology	NR	NR
Shimoyama[40]	Case report (7)	Japan	37 M	NR	Gout, right ankle fracture	Nasal RT-PCR	Supportive	Mild
Shokraee[41]	Case report (7)	Iran	58 F	Iranian	Hypertension, coronary artery disease, diabetes mellitus	Nasal RT-PCR	Interferon beta-1, Dexamethasone, Ceftriaxone, Enoxaparin, Nortriptyline	Moderate
Sinaei[42] (Patient 1)	Case series (6)	Iran	8 M	NR	None	Serology	NR	Mild
Sinaei[42] (Patient 2)	Case series (6)	Iran	6 F	NR	Hydronephrosis, right hip septic arthritis 3 years prior	RT-PCR, serology	NR	Mild
Sureja[43]	Case report (7)	India	27 F	NR	NR	Nasal RT-PCR	Methylprednisolone, Favipiravir	Moderate
Talarico[44]	Case report (8)	Italy	45M	NR	None (family history of ankylosing spondylitis)	Nasal/Oropharyngeal RT-PCR	None	Mild
Yokogawa[45]	Case report (6)	Japan	57M	Japanese	Hypertension, hyperlipidemia	Nasal RT-PCR	Supportive care	Mild vs. moderate

NR: not reported; RT-PCR: reverse transcription polymerase chain reaction; HCQ: hydroxychloroquine; ACPA: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; GERD: gastroesophageal reflux disease; JBI: Joanna-Briggs Institute critical appraisal tools; MIS-C: multisystem inflammatory syndrome in children and adolescents.

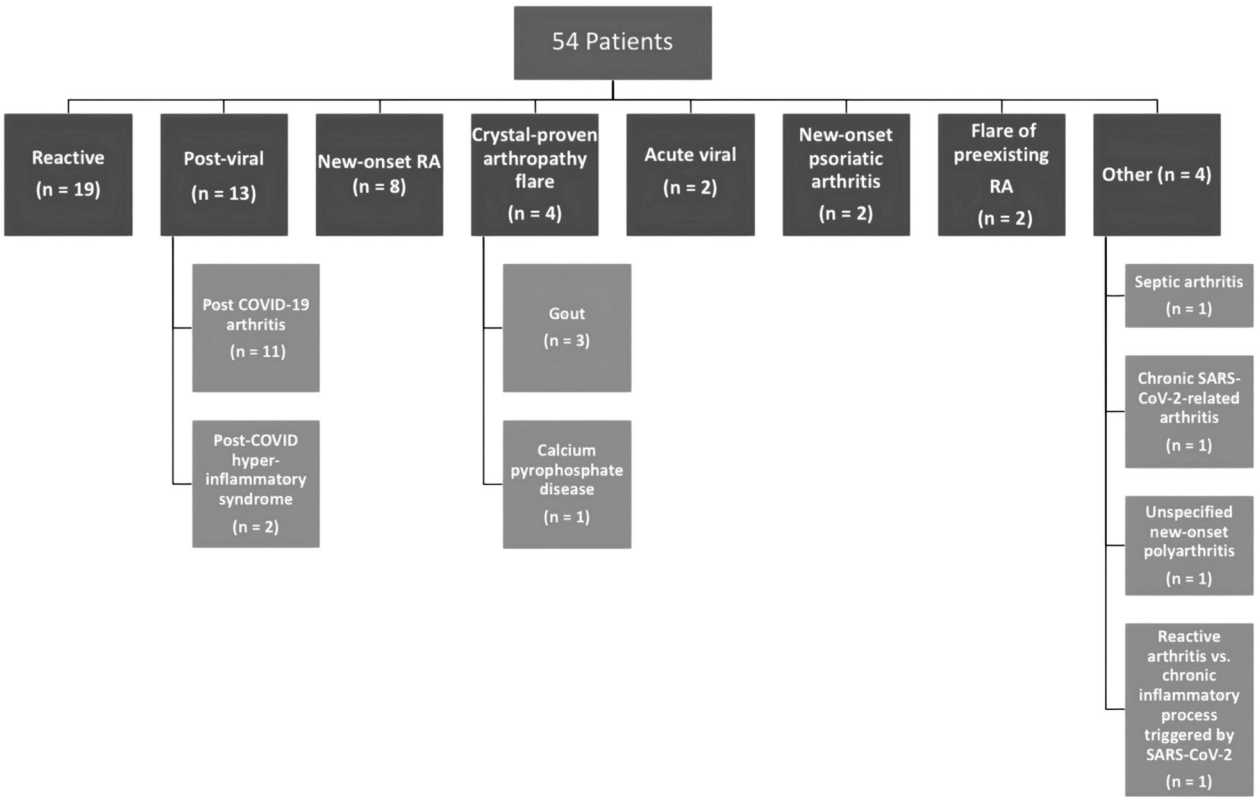

Figure 2. Classification of COVID-19-associated arthritis cases included in the systematic review.

most commonly Methotrexate, Hydroxychloroquine, and Leflunomide, were initiated in 13 cases, most of which were described as flares of preexisting rheumatic disease (e.g. RA, psoriatic arthritis) or consistent with new-onset rheumatic disease. Three patients with gout flares thought to be triggered by SARS-CoV-2 infection were treated with colchicine.[29] Approximately 11% (n = 6) of patients underwent intra-articular corticosteroid injections with or without local anaesthetics. More invasive treatments were reported in two cases.[31,40] Neves et al.[31] inserted a drainage catheter in a patient presenting with presumed septic arthritis with intramuscular collections with joint continuity noted on imaging. Shimoyama et al.[40] performed arthroscopic synovectomy in a patient with reactive arthritis that was unresponsive to a trial of NSAIDs and intraarticular steroid injection. It is important to note that most reports lacked details regarding treatment duration. Of note, one patient had no treatment rendered for their arthritis symptoms and still experienced resolution of symptoms within 4 weeks following symptom onset. The majority of authors reported symptomatic improvement or complete resolution of symptoms following treatment; however, clinical outcomes were not reported for 14 of the included cases. Resolution of articular symptoms ranged from 4 days to 5 months following onset for the cases where time to resolution was reported. The reported arthritis treatment regimens and clinical outcomes are summarized in Table 2.

DISCUSSION

The present systematic review provides a detailed summary of clinical reports of inflammatory arthritis observed both during and after SARS-CoV-2 infection. At the time of our database search, the available relevant literature was low-level evidence consisting of case reports and case series studies with a limited number of cases. Many of these cases were classified as reactive arthritis, although there were cases of new-onset psoriatic arthritis and RA as well as flares of preexisting crystal-induced arthropathy and RA reported in the literature as well. Given the arthritis presentation is suspected to be reactive arthritis, it is reasonable to assume that the COVID-19 reactive arthritis variation shares similar pathophysiology to that of other pathogens known to cause reactive arthritis. Although the relationship between SARS-CoV-2 infection and inflammatory arthritis has yet to be fully elucidated, the mechanism may involve systemic pro-inflammatory markers, such as IL-6 and TNF-α, which are known to be released in both alveolar and joint inflammation.[46] Moreover, an ecological study by Joo et al.[6] reported an association between ambient coronavirus, parainfluenza, and metapneumovirus infections and an increased rate of incident RA cases thereby, suggesting that viral respiratory infections may play a role in precipitating the onset of RA.

In the included studies, there was a slight predominance of males versus females. Moreover, patients had a mean age of 48.2 years; however, it is important to note that this demographic finding may be confounded by older patients being more likely to require medical care during and after COVID-19 infection. The overwhelming majority of patients had no documented preexisting autoimmune conditions. However, it is unclear if patients with preexisting autoimmune disease and/or preexisting chronic joint disease are more susceptible to developing acute arthritis after being infected with SARS-CoV-2. Patients in the included clinical reports had variable COVID-19 disease courses, although most of them experienced

Table 2. Clinical manifestations of acute inflammatory arthritis, diagnostic work-up, management, and outcomes.

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Alivernini[9] (patient 1)	Simultaneous onset	Unspecified new-onset polyarthritis	Polyarticular	NR	(–) ACPA/RF, ↑ CRP and cytokines	No crystals; H&E stromal activation, oedema, inflammation, and perivascular diffuse infiltrates	U/S: Joint effusion, ST thickness, increased vascularity	Etoricoxib (200 mg/d) for 4 days with worsening symptoms followed by Baricitinib (4 mg/d) and Prednisone (10 mg/d)	Progressive symptom improvement with ↓ CRP after 8 days of treatment
Alivernini[9] (patient 2)	Unclear (after respiratory symptom onset, during acute COVID-19 infection)	Flare of RA previously in sustained remission	Polyarticular	NR	↑ CRP and cytokines	U/S-guided ST biopsy: severe inflammation (infiltrates forming aggregates and few follicles) with ST thickening and fibrin exudates	U/S: Joint effusion, ST thickness, increased vascularity	IV Sarilumab (400 mg)	Significant symptom improvement and ↓ CRP and cytokines with remission achieved
Baimukhamedov[10]	5 weeks after acute COVID-19 infection onset	New-onset RA	Polyarticular	Early morning stiffness	(+) ACPA/RF; ↑ CRP and ESR	NR	NR	Methotrexate (15 mg/week) and Methylprednisolone (8 mg/d)	↓ ESR and CRP after 1 month of treatment with remission achieved after 3 months of treatment
Ben-Chetrit[11]	2 months after initial acute COVID-19 infection onset	Palindromic rheumatism followed by new-onset RA diagnosis after re-infection	Polyarticular	Early morning stiffness	(+) anti-CCP, (–) RF; borderline ANA; ↑ CRP and ESR	NR	NR	HCQ followed by Prednisone and weekly Methotrexate	No improvement with HCQ; significant improvement after initiating Prednisone and Methotrexate
Chandrashekara[12] (Patient 1)	Unclear (after acute COVID-19 infection)	Post-COVID hyperinflammatory syndrome	Polyarticular	Bilateral panuveitis, CRAO with retinitis and macular vessel vasculitis, leukoderma/ rash	(–) APLA, ANA, ANCA ↑ ferritin and D-dimer	NR	NR	Deflazacort 36 mg/d	Patient being followed at time of report
Chandrashekara[12] (patient 2)	Unclear (after acute COVID-19 infection)	Post-COVID hyperinflammatory syndrome	Unspecified joints in BLE	Significant bilateral pedal edema	↑ CRP, ESR, LDH, D-dimer, and ferritin	NR	NR	Celecoxib 200 mg BID	NR
Chandrashekara[12] (patient 3)	3 weeks after acute COVID-19 infection onset	Post-COVID-19 arthritis	Polyarticular (large and small joints of upper and lower limbs)	Early morning stiffness	↑ ESR (–) RF, anti-CCP, and ANA	NR	NR	Celecoxib	Patient responded well to NSAIDs

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Chandrashekara[12] (patient 4)	1.5 months after acute COVID-19 infection onset	Post-COVID-19 arthritis	Polyarticular (large and small joints predominantly affecting the feet)	NR	↑ ESR, CRP (–) RF, anti-CCP, and ANA (–) Chikungunya IgG	NR	NR	HCQ 200 mg BID, NSAIDs	NR
Coath[13]	Unclear (after acute COVID-19 infection)	Axial reactive arthritis	Axial (lumbar, thoracic, cervical anterior)	NR	↑ CRP (+) HLA-B27	NR	MRI: bone marrow oedema in bilateral SI joints, left 1st costovertebral and costotransverse joints Hybrid PET-CT: focal increased FDG uptake at same sites as bone marrow edema on MRI	IM Methylprednisolone 120 mg, Diclofenac 75 mg/d	Symptom resolution at 3 months with undetectable CRP and repeat MRI demonstrating near complete resolution of prior inflammatory changes
Colatutto[14] (patient 1)	1 month after acute COVID-19 infection onset	Post-COVID-19 sacroiliitis	Axial (sacroiliac)	Polymya-lgia	(–) RF, ANA, anti-SSA/SSB, and HLA-B27; ↑ CPK and cytokines	NR	MRI: Bilateral sacroiliitis with bone marrow edema	NSAIDs for 10 days and then as needed	Symptomatic improvement with mild residual low back pain; normalization of inflammatory markers
Colatutto[14] (patient 2)	1 month after acute COVID-19 infection onset	Post-COVID-19 sacroiliitis	Axial (sacroiliac)	Polymya-lgia	(–) RF, ANA, and anti-SSA/SSB; ↑ CRP and cytokines	NR	MRI: Unilateral sacroiliitis with bone marrow edema	NSAIDs as needed	Symptomatic improvement with residual low back pain; normalization of inflammatory markers
Crivelenti[15]	3 days after acute COVID-19 infection onset	Chronic SARS-CoV-2-related arthritis	Polyarticular (ankles, knees, elbows, wrists, and IP joints)	Maculo-papular rash	(–) ANA and RF; ↑ ESR, CRP, and D-dimer	NR	U/S: Synovial hypertrophy	Aspirin and 2 weeks of corticosteroids	Resolution of symptoms 5 months after onset with the exception of residual morning stiffness
Danssaert[16]	12 days after acute COVID-19 infection onset	Reactive arthritis	Monoarticular (right hand)	NR	ANA speckled; CRP, ESR, uric acid, and lactic acid WNL; (–) Lyme serology and RF; mild leukopenia and anaemia noted	NR	MRI: Inflammation around extensor tendons of 2nd, 3rd, & 4th compartments with mild synovial enhancement of tendon sheaths Doppler U/S: negative for DVT U/S: Inflammation of extensor and flexor tendons of right hand	Voltaren gel, Neurontin, Dilaudid PRN; wrist support for associated tendonitis	Pain initially improved down to 2/10 from 10/10 in severity; at time of manuscript, patient was undergoing OT and prescribed Ultram for continued pain

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Derksen[17] (patient 1)	6 weeks prior to acute COVID-19 diagnosis	New-onset RA	Polyarticular (small and large joints; upper and lower extremities)	NR	↑ ESR; CRP WNL; (+) ACPA	NR	NR	NR	NR
Derksen[17] (patient 2)	6 weeks after acute COVID-19 diagnosis	New-onset RA	Polyarticular (small and large joints; upper and lower extremities)	NR	↑ ESR, CRP; (+) ACPA	NR	NR	NR	Patient died unexpectedly during hospitaliza-tion (unclear cause of death)
Derksen[17] (patient 3)	6 weeks after acute COVID-19 diagnosis	Flare of preexisting RA previously in remission for 5 years	Polyarticular (small and large joints; upper and lower extremities)	NR	↑ ESR, CRP; (–) ACPA	NR	NR	NR	NR
Derksen[17] (patient 4)	14 weeks after acute COVID-19 diagnosis	New-onset RA	Polyarticular (small joints; upper and lower extremities)	NR	↑ ESR, CRP; (–) ACPA	NR	NR	NR	NR
Derksen[17] (patient 5)	3 days after acute COVID-19 diagnosis	New-onset RA	Polyarticular (small and large joints; upper extremities)	NR	↑ ESR; CRP WNL; (+) ACPA	NR	NR	NR	NR
De Stefano[18]	40 days after acute COVID-19 infection onset	Reactive arthritis	Monoarticular (right elbow)	3 pruritic clearly demarcated erythematous scaly patches on extensor surface of bilateral elbows and groin	(–) ANA, RF, anti-CCP, HLA-B27, and HLA-C*06	No crystals; (–) SARS-CoV-2 RNA	U/S: Findings consistent with synovitis	Oral NSAIDs, topical steroids	Complete resolution of skin and joint symptoms in 6 weeks
Di Carlo[19]	1 month after acute COVID-19 infection onset	Reactive arthritis	Monoarticular (right ankle)	NR	↑ ESR and CRP, lymphopenia; (–) HLA-B27; (–) Ureaplasma urealyticum, Mycoplasma hominis and Chlamydia trachomatis in GU system; (–) enterobacteriaceae in stool sample & serology	NR	U/S: Subtalar joint synovitis and tenosynovitis of the posterior tibial tendon sheath	Methylprednis-olone 4 mg/d	Asymptoma-tic with normalization of ESR and CRP

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Drosos[20]	1 month after acute COVID-19 infection onset	New-onset sero-negative erosive RA	Polyarticular (small joints of hands bilaterally)	Early morning stiffness; joint swelling	(–) RF, ACPA, and ANA; ↑ ESR and CRP	NR	X-ray: Erosions, joint space narrowing, soft tissue swelling U/S: Erosive lesion	Methotrexate (15 mg/week), folic acid supplement, Prednisone 10 mg/d (tapered to 2.5 mg/d after 2 months)	Substantial clinical improvement with normal acute phase reactants 2 months after treatment initiation
Fragata[21]	4 weeks after acute COVID-19 infection onset	Post-viral arthritis	Polyarticular (Right 3rd and 4th PIP joints; bilateral DIP and 1st MCP joints)	Early morning stiffness	(–) ANA, anti-ds DNA, RF, ACPA, ENAs, antibodies to echovirus, parvovirus b19, HIV 1 and 2, Hepatitis B and C; serum uric acid, ESR, and CRP WNL	NR	NR	Oral NSAIDs (Ibuprofen 1200 mg/d), 5-day course of oral Prednisolone (5 mg/d)	Improvement in symptoms by day 5 of steroid course and complete resolution of symptoms 8 weeks after symptom onset
Gasparotto[22]	4 weeks after acute COVID-19 infection onset	Post-COVID-19 arthritis	Oligoarticular (right ankle, knee, and hip)	Low-grade fever	(–) RF, ANA, and HLA-B27; ↑ CRP, ESR, D-dimer, Fibrinogen, and Ferritin	No crystals; (–) SARS-CoV-2 RNA and culture; 20000/mm^3 white blood cells	X-ray: No erosions or intraarticular calcifications	NSAIDs for ~4 weeks	↓ CRP and complete resolution of symptoms at 6-month follow-up
Hønge[23]	2 weeks after acute COVID-19 infection onset	Reactive arthritis	Oligoarticular (bilateral knees, right ankle, left foot)	Joint swelling	(–) RF, anti-CCP, ANA, HLA-B27, and HIV screening; ↑ CRP; mild leukocytosis	No crystals; (–) culture	X-ray: Fluid in joint space without evidence of arthritis	Piperacillin/ tazobactam, oral NSAIDs, Prednisolone 25 mg/d for 6 days	↓ CRP and resolution of symptoms 5 days after treatment initiation (sustained as of 4-month follow-up)
Houshmand[24]	2 days after acute COVID-19 infection onset	Reactive arthritis	Oligoarticular (bilateral knees, right elbow)	Urticaria; early morning stiffness	(–) RF and ANA; ↑ ALP; D-dimer, C3, C4, CPK, and ferritin WNL; (–) urine and stool studies	Dry tap	X-ray right elbow: unremarkable X-ray bilateral knees: bone erosions or spur, joint space narrowing, soft tissue swelling, joint effusion, osteopenia, suprapatellar effusion, and synovial thickening	Acetaminophen, Cetirizine, Desloratadine, Hydroxyzine	Resolution of joint pain and urticaria 72 hours after initiating treatment (12 days following symptom onset)
Jali[25]	3 weeks after acute COVID-19 infection onset	Reactive arthritis	Polyarticular (right 2nd/3rd PIP and 5th DIP joints; left 2nd PIP and 5th DIP joints)	NR	(–) RF, ANA, anti-CCP, hepatitis and HIV screenings; ESR and CRP WNL	NR	X-ray: Unremarkable	Celecoxib for 2 weeks	Complete resolution of symptoms after 2 weeks of treatment (sustained 2 months after discontinuation of NSAIDs)

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Kocyigit[26]	6 weeks after acute COVID-19 infection	Reactive arthritis	Monoarticular (left knee)	Early morning stiffness, joint swelling, limited range of motion	↑ ESR, CRP, and WBC; (–) RF, ANA, anti-CCP, HLA-B27; (–) urine and blood cultures	No crystals; mild inflammation; (–) culture	X-ray: unremarkable U/S: joint effusion	Diclofenac 150 mg/d (tapered after 6 weeks)	Completion resolution of symptoms and normalization of ESR/CRP following NSAID taper
Kuschner[27]	2 weeks after acute COVID-19 infection onset	Reactive arthritis	Monoarticular (right wrist)	Joint swelling	↑ ESR and CRP	No crystals; (–) gram stain and culture; (+) RT-PCR for SARS-CoV-2	X-ray: diffuse degenerative changes	Ibuprofen without relief followed by 7-day course of Naproxen-sodium	Complete resolution of pain and swelling after 4 days of therapy
Liew[28]	3 days after acute COVID-19 infection onset	Reactive arthritis	Monoarticular (right knee)	Painful glans penis with associated mild erythema and swelling	(–) HIV, syphilis, chlamydia, and gonorrhea	No crystals; (–) gram stain, gonococcal and chlamydia PCR, bacterial cultures, PCR and viral cultures for SARS-CoV-2	X-ray: Right suprapatellar effusion with mild osteoarthritic changes and joint space narrowing	Etoricoxib, Intra-articular Triamcinolone (injected 1 week after NSAIDs due to effusion recurrence)	NR
Lopez-Gonzalez[29] (patient 1)	8 days after acute COVID-19 infection onset	Acute arthritis due to crystal-proven flare (gout)	Monoarticular (1st MTP)	NR	NR	Monosodium urate crystals	NR	Intra-articular Triamcinolone with Mepivacaine, Colchicine	Flare successfully resolved
Lopez-Gonzalez[29] (patient 2)	19 days after acute COVID-19 infection onset	Acute arthritis due to crystal-proven flare (gout)	Monoarticular (ankle)	NR	NR	Monosodium urate crystals; (–) RT-PCR for SARS-CoV-2 and culture	NR	Oral Prednisone, Colchicine	Flare successfully resolved
Lopez-Gonzalez[29] (patient 3)	8 days after acute COVID-19 infection onset	Acute arthritis due to crystal-proven flare (calcium pyrophosph-ate disease)	Oligoarticular (bilateral knees)	NR	NR	Calcium pyrophosphate crystals; (–) RT-PCR for SARS-CoV-2 and culture	NR	Intra-articular Triamcinolone with Mepivacaine	Flare successfully resolved
Lopez-Gonzalez[29] (patient 4)	27 days after acute COVID-19 infection onset	Acute arthritis due to crystal-proven flare (gout)	Oligoarticular (knee and ankle)	NR	NR	Monosodium urate crystals; (–) RT-PCR for SARS-CoV-2 and culture	NR	Colchicine	Flare successfully resolved
Mukarram[30] (patient 1)	8 weeks after acute COVID-19 infection	Post-COVID-19 inflammatory arthritis resembling RA	Polyarticular (symmetrical; wrists and PIP joints)	NR	(–) RA and anti-CCP	NR	U/S: Synovitis involving wrists, MCP, and PIP joints; no bony erosions	NSAIDs (temporary relief); Prednisone 10 mg/day taper, Etoricoxib, Leflunomide 20 mg/day, and HCQ 400 mg/day	NR

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Mukarram[30] (patient 2)	6 weeks after acute COVID-19 infection	Post-COVID-19 inflammatory arthritis resembling RA	Polyarticular (symmetrical; wrists, MCP, and ankle joints)	Joint swelling	(–) RA and anti-CCP	NR	U/S: Synovitis involving wrists, MCP, PIP, ankle, and MTP joints; no bony erosions	Prednisone 10 mg/ day taper, Etoricoxib, Leflunomide 20 mg/ day, and HCQ 400 mg/day	NR
Mukarram[30] (patient 3)	8 weeks after acute COVID-19 infection	Post-COVID-19 inflammatory arthritis resembling RA	Polyarticular (symmetrical; wrists, MCP, ankles, and MTP joints)	Early morning stiffness	(–) RA and anti-CCP	NR	U/S: Synovitis involving wrists, MCP, PIP, ankle, and MTP joints; bilateral Achilles tendonitis; no bony erosions	Prednisone 10 mg/ day taper, Etoricoxib, Leflunomide 20 mg/ day, and HCQ 400 mg/day	NR
Mukarram[30] (patient 4)	10 weeks after acute COVID-19 infection	Post-COVID-19 inflammatory arthritis resembling RA	Polyarticular (symmetrical; wrists and MCP joints)	Early morning stiffness	(–) RA and anti-CCP	NR	U/S: Synovitis involving wrists, MCP, and PIP joints; no bony erosions	Prednisone 10 mg/ day taper, Etoricoxib, Leflunomide 20 mg/ day, and HCQ 400 mg/day	NR
Mukarram[30] (patient 5)	2 weeks after acute COVID-19 infection	Post-COVID-19 inflammatory arthritis resembling RA	Polyarticular (symmetrical; wrists and MCP joints)	Joint swelling	(–) RA and anti-CCP	NR	U/S: Synovitis involving wrists and MCP joints; no bony erosions	Prednisone 10 mg/ day taper, Etoricoxib, Leflunomide 20 mg/ day, and HCQ 400 mg/day	NR
Neves[31]	2 weeks after acute COVID-19 infection onset	Septic arthritis (presumed)	Oligoarticular (bilateral shoulders)	Soft tissue swelling; limited range of motion	↑ CRP; (–) blood and urine cultures	(–) Cultures for aerobic/anaerobic bacteria and Mycobacterium tuberculosis	CT: Scapulohumeral synovitis with multiple intra-muscular collections with glenohumeral joint continuity MRI: Infraspinatus and subscapular fossa collections with joint continuity	Gentamicin; drainage catheter insertion; physical therapy	Some improvement in range of motion following physical therapy
Novelli[32]	Simultaneous onset	New-onset psoriatic arthritis triggered by SARS-CoV-2 infection	Axial/ Oligoarticular (initially left ankle and left knee; followed by left knee, MTP joints, and bilateral SI joints 5 months later)	Single lesion in lumbar region resembling cutaneous psoriasis 3 months after acute infection	↑ Inflammatory markers; (–) RF, anti-CCP, ANA, and HLA-B27	(–) SARS-CoV-2 RNA; (+) anti-SARS-CoV-2 IgG	MRI Left Knee: arthritis, synovial effusion in subquadricipital recess MRI Sacroiliac: Mild bilateral sacroiliitis	Intra-articular steroid injection	NR

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Ohmura[33]	5 weeks after acute COVID-19 infection onset	New-onset psoriatic arthritis triggered by SARS-CoV-2 infection	Polyarticular (bilateral hands, shoulders, knees, and feet)	Chronic skin lesions on hands (erythema with scale; biopsy consistent with psoriasis)	↑ ESR and matrix metalloproteinase-3; (–) ANA, RF, ACPA, anti-SSA/SSB, anti-DNA, anti-Smith, anti-RNP, anti-aminoacyl-tRNA synthetase, HLA-B27; (–) Syphilis, Mycoplasma, Chlamydia pneumoniae, C. trachomatis, tuberculosis, parvovirus B19	No crystals; (–) culture	X-ray: No erosive changes or enthesophytes CT: No characteristic lesions U/S: Gray scale 2 with a power Doppler 1 signal of left radial carpal joint and left knee with effusion	Celecoxib 400 mg/d for 4 weeks (failed); Prednisolone 30 mg/d (failed); Methotrexate (failed); combination of Certolizumab Pegol 400 mg every 2 weeks, Methotrexate, and Prednisolone (remission)	Remission achieved 12 weeks after initiation of combination treatment
Ono[34]	21 days after acute COVID-19 infection onset	Reactive arthritis	Oligoarticular (bilateral ankles)	Mild enthesitis of right Achilles tendon	↑ CRP and D-dimer (–) Syphilis, HIV, ASO, Mycoplasma, Chlamydia pneumoniae, Gonococcal & Chlamydia trachomatis (urine PCR), ANA, RF, anti-CCP, and HLA-B27	No crystals; mild inflammation, (–) culture	X-ray ankle and feet: unremarkable	Intra-articular corticosteroid injection, NSAIDs	Moderate improvement
Ouedraogo[35]	7 weeks after acute COVID-19 infection onset	Reactive arthritis	Polyarticular (bilateral shoulders, left elbow, left knee)	Joint, swelling, fever	↑ ESR, CRP, WBC, and lactate; (–) blood and urine cultures; (–) RF, anti-CCP, EBV, Parvovirus B19 Enterovirus, CMV, Treponema pallidum, C. diff., HIV, Hepatitis B, Chlamydia, and Gonorrhea	No crystals; mild inflammation, (–) culture	X-ray Left Knee: Joint effusion and chondrocalcinosis	Oral Prednisolone; recurrence managed with second steroid taper and physical/occupational therapy	Significant improvement in pain and resolution of fever
Parisi[36]	25 days after acute COVID-19 infection	Viral arthritis	Monoarticular (ankle)	NR	↑ CRP, lymphopenia (–) ANA, anti-ds DNA, RF, anti-CCP, and HLA-B27	NR	U/S: Synovial hypertrophy in the tibiotarsal anterior and lateral recess, Achilles tendonitis	NSAIDs (Ibuprofen 600 mg BID)	Resolved

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Perrot[37]	25 days after acute COVID-19 infection onset	New-onset ACPA-positive RA, possibly triggered by SARS-CoV-2 infection	Polyarticular (right hand 5th MCP and IP joints; followed by spread to left hand 1st MCP and right hand 2nd/3rd MCP joints 3–5 days later)	Early morning stiffness	(+) anti-CCP2, anti-CCP3 Ab, (+) ANA, (+) anti-SSA and anti-SSB, anti-PAD4 and anti-PAD2 IgG, ↑ CRP/ESR and IL-6; borderline elevated RF and anti-DNA	NR	X-ray Hands, Wrists, and Feet: No erosion U/S: Numerous zones of cold synovitis without erosions	Methotrexate (10 mg/ week)	Good clinical response
Saricaoglu[38]	8 days after COVID-19 treatment	Reactive arthritis	Polyarticular (left foot 1st MTP, DIP, and PIP joints; followed by spread to right foot 2nd PIP and DIP joints 2 days later)	NR	↑ CRP, ferritin, and D-dimer; (–) RF, ANA, and anti-CCP; serum uric acid WNL	NR	X-ray: Unremarkable U/S Duplex: Unremarkable	NSAIDs	Complete resolution of symptoms and normalization of laboratory markers
Schenker[39]	10 days after COVID-19 symptom resolution	Reactive arthritis	Polyarticular (bilateral ankles, knees, and wrists)	Palpable purpura localized to bilateral calves	↑ CRP, (+) HLA-B27; (–) autoantibody panel; (–) unspecified serology for other acute or prior infections	NR	NR	Prednisolone	Immediate regression of symptoms and CRP levels after steroid initiation
Shimoyamo[40]	6 days after acute COVID-19 diagnosis	Reactive arthritis	Monoarticular (right ankle)	Joint swelling	↑ CRP, ESR, WBC; (–) RF, ANA, anti-CCP, HLA-B27	No crystals; marked inflammation (96,000 WBC/μL); (–) SARS-CoV-2 RT-PCR of excised synovium	MRI: Synovial hypertrophy in medial tibiotalar joint without cartilage wear CT: Bone erosion	NSAIDs (failed); intra-articular steroid injection (temporary relief followed by recurrence); arthroscopic synovectomy	No sign of arthritis recurrence postoperatively
Shokraee[41]	2 weeks after acute COVID-19 diagnosis	Reactive arthritis	Monoarticular (right hip)	Limited range of motion	↑ CRP, ESR; (–) Tuberculosis and Brucellosis	NR	U/S: Synovial hypertrophy and joint effusion MRI: Fluid rim surrounding pelvic area suggestive of hip inflammation and sacroiliitis	Indomethacin 100 mg twice daily and IM Prednisolone 80 mg	Dramatic improvement 5 days after treatment initiation with remission achieved after 14 days
Sinaei[42] (patient 1)	1 week after acute COVID-19 infection onset	Reactive arthritis	Monoarticular (left hip)	Limited range of motion	↑ CRP; normal CRP; (+) RF with low titer, (–) ANA	NR	X-ray: Unremarkable MRI: Joint effusion	Naproxen 25 mg twice daily; skin traction	Recovery achieved 1 week after treatment initiation

Table 2. Continued

Primary author	Timing of arthritis onset	Arthritis classification	Rheumatologic localization	Associated findings	Biomarkers	Synovial fluid/ tissue analysis	MSK imaging	Arthritis treatment	Outcome
Sinaei[42] (patient 2)	1 week after acute COVID-19 infection onset	Reactive arthritis	Polyarticular (bilateral knees, wrists, and left hip)	Limited range of motion	↑ CRP, ESR; (–) RF, ANA	NR	X-ray: Unremarkable U/S: Joint effusion in bilateral hips	Ibuprofen 40 mg/kg/day	Recovery achieved with normalization of U/S findings 4 days after treatment initiation without recurrence at 45-day follow-up
Sureja[43]	2 weeks after acute COVID-19 symptom onset	Reactive arthritis	Polyarticular (knees, ankles, feet, right hand)	Joint swelling	(+) RF with low titers; (–) ACPA, ANA, and HLA-B27	NR	NR	NSAIDs, Methylprednis-olone (3-week taper), opioid analgesia	Significant improvement 4 weeks after treatment initiation
Talarico[44]	1 week prior to COVID-19 symptoms; exacerbation of articular symptoms 2 months after acute infection onset	Reactive arthritis versus chronic inflammatory process triggered by SARS-CoV-2 infection	Polyarticular (bilateral hands MCP and PIP joints)	NR	↑ CPK and ESR ↑; CRP WNL; (–) RF (+) anti-CCP	NR	U/S: Slight effusion of the right wrist, bilateral effusion of 5th PIP without synovial hyperplasia	Methylprednisolone (starting from 16 mg with progressive taper)	Complete resolution of articular symptoms during steroid course; slight exacerbation of arthralgia after discontinuing steroid taper at time of manuscript
Yokogawa[45]	17 days after acute COVID-19 infection onset	Viral arthritis	Oligoarticular (left wrist, right shoulder, bilateral knees)	NR	↑ CRP; (–) ANA, RF, anti-CCP, hepatitis B surface antigen, anti-hepatitis C virus Ab, and HIV Ab	No crystals; (–) SARS-CoV-2 RNA	NR	None	Spontaneous resolution of articular symptoms on day 27

NR—not reported; ANA—antinuclear antibody; ACPA/anti-CCP—anti-cyclic citrullinated peptide antibody; APLA—antiphospholipid antibody; ANCA—antineutrophil cytoplasmic antibodies; HLA—human leukocyte antigen; CRAO—central retinal artery occlusion; RF—rheumatoid factor; CRP—C-reactive protein; ESR—erythrocyte sedimentation rate; U/S—ultrasound; MRI—magnetic resonance imaging; WNL—within normal limits; NSAIDs—nonsteroidal anti-inflammatory drugs; ST—synovial tissue; OT—occupational therapy

mild-to-moderate COVID-19 infection. Treatment regimens ranged from supportive care alone to antivirals with or without adjunct antibiotics or hydroxychloroquine.

The onset of arthritis symptoms in the reviewed cases varied considerably with the mean onset being approximately 4 weeks after COVID-19 symptoms began with the exception of cases that had preceding joint symptoms prior to other COVID-19 symptoms and those with an unspecified symptom onset. The rheumatologic localization for the majority of cases was polyarticular. There was considerable variability in terms of the joints involved. The variation in clinical presentations lead to the authors classifying COVID-19 associated arthritis in a number of different ways. Some authors termed the presentation 'post-COVID hyperinflammatory syndrome', whereas others diagnosed their patients with 'post-COVID-19 arthritis.' When the presentation of the arthritis symptoms manifested concurrently with COVID-19 symptoms, the authors often classified it as an unspecified new-onset polyarthritis. When the arthritis symptoms clearly started after the onset of COVID-19 symptoms and in most cases following resolution of COVID-19 symptoms, the authors diagnosed it as reactive arthritis or post-viral arthritis. Most of the cases included in this review were classified as either reactive arthritis or post-viral arthritis, although there were also several cases of new-onset RA thought to be triggered by COVID-19.

In terms of associated extra-articular findings, six patients had cutaneous findings, including maculopapular rash, urticaria, lesions consistent with psoriasis, palpable purpura, pruritic clearly demarcated erythematous scaly patches, and leukoderma with an associated unspecified rash. Interestingly, there were no cases of keratoderma blennorhagicum, classically presenting as painless vesiculopustular waxy lesions localized to the palms/soles; this cutaneous finding is estimated to occur in approximately 5–30% of reactive arthritis cases.[47] In a single case described by Liew et al.,[28] a patient presented with pain localized to the glans penis with mild erythema and swelling. However, there were no cases of patients presenting with the classic triad of reactive arthritis formerly termed 'Reiter's syndrome' (conjunctivitis, arthritis, and non-infectious urethritis), albeit it has been estimated that only up to one-third of patients with reactive arthritis present with all three classic findings.[48] Of note, Santacruz et al.[49] described an unusual case of reactive arthritis 2 months after acute COVID-19 infection presenting exclusively with extra-articular findings, including conjunctivitis, oral aphthous ulcers, palatal erosions, keratoderma blennorhagicum, and vulvitis without evident arthritis.

Although the diagnostic work-up in these cases was quite variable, many authors used both normalization of ESR and CRP and symptomatic improvement to determine treatment efficacy. Among cases where synovial fluid analyses were performed, the predominant finding was lack of crystals with H&E showing stromal activation, oedema, inflammation, and perivascular diffuse infiltrates. Moreover, there were mixed findings for synovial fluid testing positive or negative for SARS-CoV-2 RNA or antibodies. Authors who elected to obtain imaging of the affected joints often reported findings suggestive of non-specific inflammation, including joint effusion, synovial tissue thickening, and increased vascularity.

The treatment rendered for arthritis symptoms, regardless of geographic or demographic characteristics, consisted largely of NSAIDs. Corticosteroids were a close second with a majority of patients receiving both NSAIDs and corticosteroids. Corticosteroids were administered topically, orally, intra-articularly, or intramuscularly. Given the limitations of the review, it is difficult to definitively say which route of administration was the most clinically effective. Regardless of the administration route, corticosteroids played a crucial role in many of the cases with some patients failing to experience any symptomatic improvement until steroids were initiated. DMARDs were initiated in 13 cases, most of which were described as either flares or new-onset of rheumatic disease (e.g. RA, psoriatic arthritis), with good clinical response noted in the majority of cases. Intraarticular corticosteroid injections were performed in approximately 11% of cases. More invasive treatment measures, including surgical intervention, were reported only in a minority of cases. Resolution of articular symptoms ranged from 4 days to 5 months following onset. However, not all authors reported time to symptom resolution and some patients were still being followed at the time of publication, thereby making it impossible to ascertain how many patients had refractory symptoms or long-term sequelae. It is worth noting that in the existing literature on reactive arthritis, it has been reported that most patients have a self-limited disease course, whereas 15–30% may go on to have chronic or refractory symptoms.[50] Moreover, there have been reports of symptomatic improvement following initiation of DMARDs among patients with chronic symptoms, although it is important to note that use of DMARDs or biologics in cases of reactive arthritis refractory to steroids and NSAIDs may not lead to a good clinical response in all cases.[51]

Limitations

This systematic review is not without its limitations. First, given that SARS-CoV-2 is still a relatively novel virus, there were only a limited number of clinical reports examining the potential association between COVID-19 infection and the development of acute inflammatory arthritis published when this systematic review was performed. Second, the studies published in the available literature are considered low-level evidence given that most are clinical case reports. Third, given the nature and brevity of case reports, some of the included articles lacked clinically relevant information, which limited our qualitative data synthesis. Fourth, there appear to be discrepancies in the nomenclature and classification of arthritis cases used by the authors. It is also important to note that different SARS-CoV-2 variants may be associated with different clinical presentations of inflammatory arthritis. Finally, although substantial effort was made to ensure that all relevant studies published at the time of the database search were included in this review, it is still possible albeit unlikely that relevant eligible studies were excluded.

Conclusion

Given the widespread impact of the COVID-19 pandemic, it is imperative for clinicians to not only have an understanding of how this disease affects patients acutely but to be cognizant of its longer-term sequelae, including its potential role in the precipitation of autoimmune and rheumatologic conditions. While the available literature does not allow for determination of causal associations, there is limited low-level evidence suggesting that patients may develop inflammatory arthritis during and after SARS-CoV-2 infection. Therefore, in the era of COVID-19, clinicians should consider including

this in their differential diagnosis for patients presenting with new-onset inflammatory arthritis during or after acute SARS-CoV-2 infection. Needless to say, the present systematic review highlights the paucity of research in this area and a need for the emergence of high-level evidence to fully elucidate the relationship between SARS-CoV-2 infection and the development of inflammatory arthritis.

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N/A

Supplementary material

Supplementary material is available at *Family Practice* online.

Author contribution

All authors contributed to the design of this protocol. ZSC and NN initiated the project. The protocol was drafted by ZSC and was reviewed and refined by AS and CR. ZSC and NN performed the literature search, data collection, and qualitative synthesis. All authors contributed to interpretation of data. ZSC and NN were responsible for drafting the manuscript. All authors contributed intellectual content, revised the manuscript, and approved the final draft for submission. ZSC serves as the guarantor and corresponding author for this manuscript.

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Conflict of interest

None declared.

Data Availability

The data underlying this article are available in the article and/or in its online supplementary material.

Registration

N/A

Protocol

Not prepared.

Ethics approval

N/A—this study did not require IRB approval as it is a systematic review.

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