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Exploring Epidemiological, Clinical, and Autoimmune Reactivity Perspectives of Rheumatoid Arthritis After COVID-19

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ABSTRACT

Background: Emerging evidence suggests that SARS-CoV-2 infection may contribute to the development or exacerbation of autoimmune diseases, including rheumatoid arthritis (RA), through mechanisms such as immune system hyperactivation, cytokine storm, and the production of autoantibodies.

Materials and Methods: This review aimed to investigate the potential association between SARS-CoV-2 infection or vaccination and the onset or flare-up of RA, with a focus on pathogenic mechanisms, clinical features, diagnostic approaches, and therapeutic strategies. A collection of published case reports and studies was reviewed to identify patterns and clinical outcomes related to RA after COVID-19 infection or vaccination.

Results: New-onset RA symptoms are most frequently observed within 2 to 16 weeks post-infection, with a higher incidence in women. Common laboratory findings included elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels, along with positive rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). In some cases, a genetic predisposition was also identified, suggesting an interaction between genetic and environmental factors. Despite the viral context, diagnosis and treatment strategies are largely aligned with standard RA protocols. RA onset or exacerbation following COVID-19 vaccination appears to be rare, and the benefits of vaccination continue to outweigh the associated risks.

Conclusion: Although current evidence suggests a potential association between SARS-CoV-2 infection and the pathogenesis of RA, existing studies are limited in scope and sample size. Further large-scale, longitudinal research is required to substantiate these findings and better understand the underlying mechanisms.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was first identified in December 2019 in China. The virus spread rapidly worldwide, leading to an unprecedented global crisis. As a result, the World Health Organization (WHO) declared it a global pandemic on March 11, 2020 [1, 2]. The range of symptoms of this disease is extensive, varying from asymptomatic cases to severe respiratory disorders and even organ failure [3]. More severe and critical forms of the disease can disrupt the immune system and trigger severe inflammatory conditions, such as cytokine storms, lymphocyte reduction, and multi-organ failure, which threaten the survival of patients, especially older people and those with underlying health conditions [4, 5].

Rheumatoid arthritis (RA) is a chronic autoimmune condition characterized by continuous inflammation of the synovium, damage to the joints, and gradual joint destruction, most often affecting joints such as the metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal, knees, and wrists [6]. While early explanations for its pathogenesis were based on immune complexes, recent discoveries highlight the central role of autoantibodies, such as anti-citrullinated protein antibodies (ACPA), and various immune mechanisms involving T cells and cytokine networks that drive destructive joint changes [7, 8].

The emergence of COVID-19 and its wide-ranging impact on the immune system have opened new avenues for studying how infections influence autoimmune diseases. Many post-COVID patients continue to suffer from long-lasting musculoskeletal issues, such as joint pain and arthritis [9]. Emerging evidence suggests that COVID-19 may provoke excessive activation of the immune system and the production of autoimmune antibodies, leading to autoimmune conditions like RA, especially in genetically susceptible individuals. These cases are often associated with elevated titers of RF and ACPA, suggesting a potential link between the virus and RA [10, 11].

In the present study, we investigate the prevalence and clinical manifestations of RA following SARS-CoV-2 infection and the clinical implications related to the management and treatment of affected patients, which will ultimately contribute to a clear idea of the association between COVID-19 and the possibility of developing autoimmune rheumatological diseases, especially RA.

Materials and Methods

Aiming to identify studies related to the onset or exacerbation of RA following COVID-19 infection or vaccination, this review article involved a literature search in PubMed, Web of Science, and Google Scholar using the keywords “rheumatoid arthritis,” “autoimmunity,” “SARS-CoV-2,” “vaccination,” and their corresponding MeSH terms. Articles published from 2019 onward were included in the review.

COVID-19, a trigger for autoimmunity

Several studies have explored the role of cytokine storms and immune dysregulation in the development of autoimmune diseases following COVID-19 infection. These studies demonstrate that excessive immune activation and dysregulated immune responses in COVID-19, characterized by the overproduction of cytokines and the development of a cytokine storm, contribute to the generation of autoimmune antibodies, inflammation, and tissue damage [12-14]. These processes are similar to the mechanisms seen in RA and other autoimmune disorders. They can ultimately lead to loss of immune tolerance and an increased likelihood of the onset of diseases such as RA, systemic lupus erythematosus, and vasculitis [15, 16].

Numerous compelling theories suggest that SARS-CoV-2 and other viruses could play a significant role in triggering autoimmune responses through mechanisms such as molecular mimicry, epitope spreading, bystander activation, viral persistence, the release of sequestered self-antigens or hidden antigens, and superantigen activation [17-19]. One of the main hypotheses is molecular mimicry. According to this hypothesis, SARS-CoV-2 antigens may show relative similarity to antigens associated with RA and, in the severe inflammatory environment caused by COVID-19, accompanied by high levels of cytokines and antibodies, stimulate an immune response against host tissues, leading to autoimmune diseases in the affected individual [20]. For instance, studies reported the presence of a shared heptapeptide (LDKYFKN) between the SARS-CoV-2 spike protein and a human protein (follistatin-related protein 1) in patients with autoimmune diseases such as systemic lupus erythematosus and RA [21, 22]. Additionally, another study has shown that several hexapeptides from SARS-CoV-2 proteins, particularly the spike, exhibit high sequence similarity with human peptides, and this mechanism may trigger immune cross-reactivity and contribute to the onset or worsening of autoimmune diseases [23]. Overall, the presence of mechanisms such as

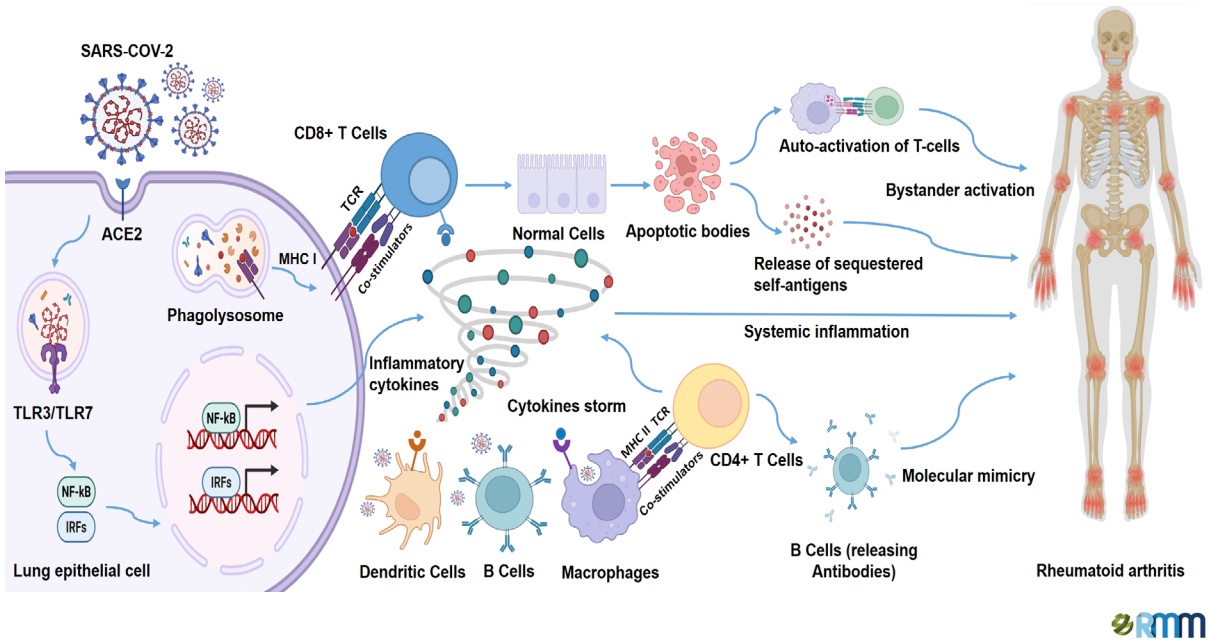

Figure 1. The SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) receptors expressed on host cells surface, subsequently replicating within them

molecular mimicry, bystander activation, and release of sequestered self-antigens in the highly inflammatory environment induced by SARS-CoV-2 infection can create favorable conditions for the initiation or exacerbation of autoimmune diseases (Figure 1).

This entry activates intracellular inflammatory signaling pathways such as NF-κB and IRFs, leading to the extensive release of inflammatory cytokines and the development of systemic inflammation, which can create a context conducive to the initiation of autoimmune responses. Concurrently, viral components activate antigen-presenting cells (APCs), including macrophages, dendritic cells, and B cells. These APCs present viral antigens to CD4+ T cells, resulting in their activation, increased cytokine secretion, amplification of the cytokine storm, and the production of antiviral antibodies. In this highly inflammatory environment, molecular mimicry phenomena may occur, whereby antibodies mistakenly target self-antigens that resemble viral antigens. Simultaneously, activation of CD8+ T cells via interaction with major histocompatibility complex (MHC) class I molecules enables these cytotoxic lymphocytes to recognize and eliminate infected cells. However, in an intensely inflammatory setting, bystander activation can occur, where CD8+ T cells become nonspecifically activated and subsequently destroy neighboring uninfected cells. The destruction of both infected and uninfected cells results in the release of sequestered self-antigens, or hidden antigens, into the extracellular environment. Under prevailing inflammatory conditions, these self-antigens are exposed to the immune system and may serve as triggers for autoimmune responses.

On the other hand, viral infections can expose hidden antigens or alter proteins through processes such as citrullination, which may trigger an autoimmune response. In particular, diseases caused by SARS-CoV-2 have been linked to the production of antibodies against cyclic citrullinated peptides (CCP) and peptidyl arginine deiminase (PAD). Proteins that are vulnerable to the effects of PAD are released when cells undergo apoptosis or necrosis during an inflammatory condition [24, 25]. Studies have shown that specific antibodies associated with RA, such as anti-CCP2 and anti-PAD4, are increased in patients with COVID-19 [15]. These findings are consistent with previous studies, which have shown that anti-PAD4 antibodies are present in 20% to 40% of patients with anti-CCP-positive RA [26].

Prevalence of RA following COVID-19

RA, with 17.9 million people living with the condition and an annual incidence of 488269 new cases, is one of the most common chronic inflammatory joint diseases worldwide [27, 28]. Based on the systematic and comprehensive analysis of the global burden of disease (GBD) study conducted on 2021 data, it was shown that the three regions of Andean Latin America, Central Latin America, and Australasia had the highest rates of age-standardized prevalence rate (ASPR) and age-standardized incidence rate (ASIR) of RA, while

Oceania, Western Sub-Saharan Africa, and Southeast Asia had the lowest rates of ASPR and ASIR. Moreover, the ASPR and ASIR in Andean Latin America, Southern Latin America, North Africa, and the Middle East have increased compared to the past. In contrast, the ASPR and ASIR in Southern Sub-Saharan Africa, high-income Asia Pacific, and Tropical Latin America have decreased over time [28]. Although there are limited studies examining the extensive and regional prevalence of RA following COVID-19 infection, a retrospective cohort study conducted in Colombia reported a significant increase in the diagnosis of inflammatory arthritis, including RA, during the pandemic (2020-2022). In this large-scale study conducted on the Colombian population, the incidence of RA, including serological RA and unspecified RA, increased during the COVID-19 pandemic. The relative incidence rates, in this study, were 1.60 for serological RA, 2.93 for nonspecific RA, and 2.01 for RA overall [29]. These findings suggest that COVID-19 may trigger the development of RA, particularly in the first year after infection.

Studies indicate that the risk factors for RA can be categorized into two main groups: Host-related factors, including genetic, epigenetic, hormonal, and comorbid conditions; and environmental factors, such as smoking, infections, diet, air pollution, and socioeconomic determinants [30]. According to emerging data, respiratory virus infections may raise the likelihood of developing autoimmune inflammatory disorders like RA and even aggravate disease activity in those who already have inflammatory arthritis [31, 32]. As a result, SARS-CoV-2 infection might contribute to the onset of RA or exacerbate its symptoms [15, 33]. Several case studies have also reported an increased prevalence of RA following COVID-19 infection and observed that RA after COVID-19 may prevail in different periods. For instance, three females (aged 27, 55, and 62) with no history of autoimmune disease developed symptoms of inflammatory arthritis 12 to 16 weeks after contracting COVID-19 [34]. In another case, a 67-year-old male was diagnosed with RA, showing elevated RF and ACPA antibodies, only one month after recovering from severe COVID-19 [11]. Similarly, after recovering from COVID-19, a 63-year-old male with other health problems started showing symptoms of RA, which was confirmed 2 months later [35]. In addition, a 38-year-old female developed seropositive RA one month and a 72-year-old female 2 weeks after recovering from COVID-19 [10, 36]. Also, the risk of developing RA after COVID-19 varies by age and sex. Women aged 51–60 years had the highest risk ratio for developing RA, while the risk was significantly lower in men [29]. These findings are consistent with known demographic patterns of RA and suggest that COVID-19 exacerbates existing vulnerabilities in these groups.

Studies have shown that, in addition to environmental factors, genetic factors also play a significant role in the development of RA. Genes within the MHC are estimated to contribute approximately 37% to this disease susceptibility [37]. Specifically, certain human leukocyte antigen (HLA) loci, most notably HLA-DRB1, are strongly associated with severe RA across diverse populations [38, 39]. Also, Studies have further indicated that the distribution of shared epitope (SE)-coding HLA-DRB1 alleles varies across populations. For instance, in Europeans, DRB1*04:01, *04:04, and *01:01 are common risk alleles, while DRB1*04:05 and 09:01 are prevalent in East Asians. DRB1*14:02 has been linked to severe RA in several Native American groups [40-42]. Moreover, in one case study, a 72-year-old female developed arthritis 15 days after an asymptomatic COVID-19 infection. Genetic analysis revealed the presence of HLA-DRB1*04:11, HLA-DQB1*03:01, and HLA-DQB1*03:02 alleles, which may indicate a predisposition factor for RA and suggest that COVID-19 acted as an environmental trigger [10]. Notably, however, not all post-COVID RA cases occur in genetically predisposed individuals [15]. This condition indicates that a constellation of environmental and genetic factors, along with multiple deregulatory mechanisms, contributes to the pathogenesis of RA following COVID-19.

Clinical manifestations of RA following COVID-19

Some case reports have shown that RA may emerge after a COVID-19 infection, particularly several weeks or months after recovery from the disease. Clinical data indicate that joint complaints usually appear 2 to 16 weeks after SARS-CoV-2 infection and, in most cases, resemble new-onset RA. Clinical manifestations include symmetric polyarthritis, which often affects the small joints of the hands and feet, and is accompanied by symptoms such as pain, swelling, and stiffness. In addition, inflammation is commonly seen in large and small joints, such as the MCP joints, PIP joints, wrists, and knees, which are similar to those seen in classic RA [34]. Several case studies have shown these joint problems. For instance, one case involved a 72-year-old female who began experiencing symmetric polyarthritis just two weeks after an asymptomatic COVID-19 infection. She had swelling and tenderness in several joints, including those in her hands (the MCP and PIP joints), wrists, and knees [10]. Similarly, a 60-year-old female reported pain and swell-

ing in the MCP and PIP joints of her hands following her recovery from COVID-19, and a 67-year-old male developed symmetrical polyarthritis in both his knees and hands one month after being diagnosed with the virus [11, 15]. In addition to joint swelling and pain, some patients have also experienced systemic inflammatory symptoms. These include morning stiffness, a noticeable reduction in passive joint mobility, myalgia (muscle pain), and tenosynovitis (inflammation of the tissue around tendons). Such symptoms can develop rapidly over just a few weeks [11, 35].

Beyond joint involvement, patients with RA who have followed COVID-19 often exhibit elevated inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [10, 11, 34, 35, 43]. Autoimmune antibodies, including RF and ACPA, are frequently detected in these cases, aiding in the confirmation of an RA diagnosis. While autoantibodies such as RF and ACPA are reliable biomarkers for RA, one study did not report a significant increase in ACPA positivity in post-COVID-19 patients, except among those with previous RA [44]. However, all other studies have detected RA-related autoantibodies in cases of RA developing after SARS-CoV-2 infection, particularly in severe cases [10, 11, 34-36, 45]. Additionally, one study has confirmed that COVID-19 patients sometimes exhibit RA-related antibodies, including IgM-RF and IgA-RF, in approximately 20% of COVID-19 cases, particularly in severe cases [46].

Diagnostic challenges

RA diagnosis typically involves a combination of clinical evaluation, physical examination, serological tests, and imaging. Ultrasound and MRI imaging are very valuable for observing synovial inflammation. Ultrasound is particularly useful in identifying subclinical synovitis and early bone erosion, which may predict disease progression even in the presence of clinical improvement. On the other hand, markers such as CRP, ESR, and RA-specific antibodies, including ACPA and RF, play a central role in the diagnostic process [47-49].

The established methods for diagnosing RA following COVID-19 remain fundamentally unchanged. However, it is essential to note that the differential diagnosis of RA from other diseases, such as osteoarthritis, viral polyarthritis, and autoimmune conditions like reactive arthritis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, fibromyalgia, and mixed connective tissue disease, now requires greater caution following COVID-19 [9, 34]. Imaging techniques and serology tests play a crucial role in diagnosing RA after SARS-CoV-2 infection, as the clinical manifestations of this disease may overlap with those of other inflammatory conditions, such as reactive arthritis [9]. Radiological imaging, particularly x-rays, is a commonly employed diagnostic tool; however, it may not detect joint erosion in the early phases of RA. Instead, periarticular osteopenia, indicative of reduced bone density surrounding the joint, is more frequently observed [34]. In comparison, ultrasound often detects synovitis and tenosynovitis in multiple joints, with Doppler signals indicating active inflammation, even when x-rays do not reveal erosive changes [15, 34].

In addition to the common imaging techniques mentioned, the levels of RA-specific antibodies, along with inflammatory markers, were examined in these patients. Some studies have identified an increase in ACPA and RF concerning the onset of RA [10, 11, 34-36, 45]. Moreover, elevated inflammatory markers such as ESR and CRP have been reported in some RA patients [10, 11, 34, 35, 43]. Although these markers are nonspecific for RA, their presence, alongside specific serological indicators such as ACPA and RF, along with confirmatory imaging studies, can support the diagnosis of RA. Also, in one of the reported cases, it was shown that in the absence of classic RA symptoms, inflammatory markers were elevated and ACPA and RF were positive, which ultimately led to the diagnosis of RA [9]. These case reports highlight the diagnostic complexity of RA after COVID-19, which requires greater attention to differential diagnosis, serological nuances, and the use of advanced imaging techniques.

Management and treatment

The management of RA that occurs after a COVID-19 infection is based on standard RA treatment protocols, which have remained largely unchanged. However, it is emphasized that these protocols are revised to address the unique conditions following viral infection, with differences arising from the specific pathophysiology and triggers associated with the SARS-CoV-2 virus. This management requires a targeted strategy that incorporates a range of corticosteroids, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, and supportive therapies. Corticosteroids have played an important role in the initial management of RA after COVID-19. The use of high-dose intravenous pulses in the early stages, followed by a gradual reduction to an oral form, has produced notable results. In one case, a 72-year-old female showed improvement after three days of intravenous methylprednisolone (250 mg/d for three days) and oral prednisolone (15 mg/d) [10]. In a

similar case, a 63-year-old male showed improvement with 40 mg/day of prednisolone, and a combination of naproxen, paracetamol, amitriptyline, and a tapering plan was used to lower long-term risks [35].

Methotrexate, as a DMARD, has been widely used to control disease in RA after COVID-19. In several cases, treatment was initiated with an initial dose of 10 to 15 mg per week, and in some cases, it was increased to 20 mg per week to achieve better disease control. Methotrexate was associated with a reduction in disease activity or achieving clinical remission within a few months [10, 11, 34]. In addition to the cases mentioned earlier, the combination of corticosteroids with methotrexate has shown better results compared to monotherapy. For example, in a case report, it was demonstrated that despite initially high disease activity, patients achieved recovery with these combinations and showed marked improvement shortly after the start of treatment [11, 34].

Non-steroidal anti-inflammatory drugs (NSAIDs) are also used for milder symptoms or as an extra treatment. For example, a 38-year-old female with seropositive RA improved with a mix of NSAIDs and methotrexate [36].

Corticosteroids are considered stronger anti-inflammatory drugs than NSAIDs, but they have more side effects compared to NSAIDs. For this reason, they are only prescribed for a short period at low doses and during exacerbations or flare-ups of RA. The use and prescription of corticosteroids should be carried out with greater caution during the pandemic [50, 51]. In some cases, prednisolone was tapered over weeks or months, depending on disease activity and inflammation levels. Ongoing assessment using DAS28 scores and inflammation markers, such as CRP and ESR, is key. If the treatment doesn't work well, the methotrexate dose may be increased, or other DMARDs may be tried [11, 34, 35].

In summary, traditional RA treatments remain effective post-COVID-19, but they need to be adapted to the post-viral conditions. The rapid initiation of DMARDs, cautious use of glucocorticoids, and consideration of cytokine-based therapies are the main components of this management.

The role of the COVID-19 vaccine in the possible onset of RA

The likelihood of developing RA or other joint-related diseases after receiving the COVID-19 vaccine has become a topic of increasing attention and concern. While vaccines have played an important role in controlling the COVID-19 pandemic, reports of new autoimmune and auto-inflammatory diseases, including RA, have been published in a limited number of cases. According to a systematic review of 31 studies, arthritis occurred in 84.4% of cases following vaccination with either the adenovirus vector (ChAdOx1) or mRNA (BNT162b2, mRNA-1273) vaccines. In the meantime, most patients experienced pain, swelling, and limited joint movement, with multiple joints affected, within a week after the vaccine [52]. Moreover, several case studies have documented the onset and clinical features of RA after COVID-19 vaccination (Table 1).

Further evidence from other studies, including one that documented new cases of RA, vasculitis, and lupus after vaccination, suggests that there may be a link between the vaccine and the flare-up of autoimmune diseases. In these cases, symptoms appeared a few days after immunization and improved with glucocorticoids and immunosuppressive drugs [59]. Although some research has raised concerns regarding the risk of flare-ups in autoimmune diseases such as RA following COVID-19 vaccination, studies show contradictory results in this area. A meta-analysis, which included 9874 inflammatory arthritis patients, found no significant overall increase in joint disease flare-ups following COVID-19 vaccination when comparing RA patients with those with spondyloarthritis. Still, it did show an increased risk of joint flares in a subgroup of patients with psoriatic arthritis compared to those with RA [61]. Nonetheless, the possibility that vaccination could trigger or worsen autoimmune diseases, particularly in those with a history of inflammatory joint issues, has not been fully excluded. While the link between COVID-19 vaccination and the onset or flare-up of RA is not yet fully understood, current data suggest that these cases are uncommon. However, vaccination is necessary for COVID-19 management, and for the majority, the benefits outweigh the risks involved.

Conclusion

Some existing evidence suggests an association between SARS-CoV-2 infection and the onset or exacerbation of RA, an issue that has important implications for the field of rheumatology and public health. However, extensive and long-term research is essential to investigate the prevalence of RA after COVID-19. Additionally, having a better understanding of how the immune system reacts, especially through increased autoantibodies, the citrullination process, and genetic factors such as HLA, could help improve the diagnosis and treatment of RA that appears after COVID-19. On the other hand, developing predictive models using epidemiological data

Table 1. Onset and clinical features of RA after COVID-19 vaccination

Conducted Study, Author(s), Year	Country	Demographic Information		Vaccine		Symptoms (Joint-Related)	Onset of symptoms After Receiving the Last Dose
		Age (y)	Gender	Type	Dose		
Baimukhamedov et al. 2021 [53]	Kazakhstan	38	Female	Adenovirus (SPUTNIK-V)	1	Pain and stiffness in both shoulder and knee joints	20 days
Watanabe et al. 2022 [54]	Japan	53	Male	mRNA (BNT162b2)	2	Swelling and pain in the left knee, bilateral omalgia, and morning stiffness	4 weeks
Nahra et al. 2022 [55]	USA	74	Male	mRNA (Pfizer-BioNTech)	1	Bilateral hip and shoulder pain, left thumb pain, polyarthralgia, rash over multiple joints.	10 days
Yonezawa et al. 2022 [56]	Japan	54	Male	mRNA (Pfizer-BioNTech)	2	Swelling and pain in the joints with tenderness in each joint, polyarthritis	1 day
Singh et al. 2022 [57]	India	50	Female	Inactivated (BBV152)	1	Bony nodules near both elbows, followed by severe pain and swelling in the elbows, wrists, MCP, and PIP joints while sparing the DIP joints.	7 days
Emran et al. 2022 [58]	USA	81	Female	mRNA (Moderna)	2	Unilateral synovitis, tenosynovitis, and diffuse swelling in the right wrist/hand	3 weeks
Matsuda et al. 2024 [59]	Japan	79	Female	mRNA (BNT162b2)	2	Swelling and pain in finger joints and both ankle joints, polyarthritis with joint swelling and tenderness	2-3 days
Almouslem et al. 2024 [60]	Oman	32	Female	mRNA (Pfizer-BioNTech)	2	Severe joint pain and swelling	1 week

Conducted Study, Author(s), Year	Clinical Data		Treatment	Outcome
	Imaging Diagnosis	Laboratory Tests		
Baimukhamedov et al. 2021 [53]	Ultrasound: Moderate effusion in the knees, MCP, and PIP joints. X-ray: No evidence of lesions.	RF: 170 IU/mL, ACPA: 157 U/mL, ESR: 39 mm/h, CRP: 10 mg/L	Methotrexate (15 mg per week), NSAIDs, methylprednisolone (100 mg daily infusion for 3 days)	Improved
Watanabe et al. 2022 [54]	MRI: Diffuse knee effusion.	RF: 51 IU/mL, ACPA: 1200 U/mL, CRP: 8.45 mg/dL	Methotrexate (3 mg per day, gradually increasing), prednisolone (5 mg per day), subcutaneous etanercept injection (50 mg per week), subcutaneous tocilizumab injection (162 mg per week)	Improved
Nahra et al. 2022 [55]		RF: 24 IU/mL, ACPA: Negative, CRP: 15 mg/L, ESR: 6 mm/h	Prednisolone (initial dose 20 mg per day), increased to 30 mg, followed by leflunomide (due to contraindications of methotrexate)	Improved
Yonezawa et al. 2022 [56]	X-ray: No evidence of erosions or joint space narrowing	RF: 1,712 IU/mL, ACPA: 162 U/mL, CRP: 3.69 mg/dL	Methylprednisolone 8 mg per day, iguratimod 25 mg per day	Improved
Singh et al. 2022 [57]		RF: 68 IU/mL, ACPA: 279 U/mL, CRP: 47 mg/L	Prednisolone 10 mg per day, reduced to 5 mg per day, methotrexate 7.5 mg per week	Improved
Emran et al. 2022 [58]	MRI: Synovitis, erosion, and tenosynovitis in the right wrist. X-ray: Osteopenia and mild osteoarthritis in the wrists and knees.	RF: Negative, ACPA: Negative, ESR: 104 mm/h CRP: 4.8 mg/dL	Methotrexate (initially 10 mg, increased to 15 mg per week)	Improved
Matsuda et al. 2024 [59]	Ultrasound: Synovitis in wrist and finger joints. X-ray: No evidence of erosion.	RF 59 IU/mL, ACPA: 184.6 U/m, ESR: 95 mm/h, CRP: 10.9 mg/dL	Prednisolone 10 mg per day, abatacept (125 mg, weekly), followed by tofacitinib, baricitinib, sarilumab, and tacrolimus	Deceased (COVID-19)
Almouslem et al. 2024 [60]		RF: 72 IU/mL, ACPA: >200 U/mL, CRP: 15 mg/L	Intramuscular methylprednisolone injection, hydroxychloroquine, and reduction of prednisolone dosage	Improved

Abbreviations: ACPA: Anti-citrullinated protein antibodies; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MRI: Magnetic resonance imaging; RF: Rheumatoid factor.

and clinical characteristics of patients can help identify individuals at risk and design targeted interventions. Considering the likelihood of RA as a late consequence of COVID-19, long-term monitoring of recovered patients, identification of reliable biomarkers, and evaluation of the potential protective role of COVID-19 vaccines should be prioritized in future research agendas. Raising awareness among health professionals about this connection and adopting comprehensive approaches in patient care will be crucial for reducing the burden of autoimmune diseases in the post-COVID era.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Study design and supervision: Alireza Rafiei; Data collection and writing the original draft: Ali Yousefian Zahra Yazdani; Review and editing: Zahra Yazdani.

Conflict of interest

The authors declared no conflict of interest.

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