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Review Article

The COVID-19 Pandemic Heightens Interest in Cytokine Storm Disease and Advances in Machine Learning Diagnosis, Telemedicine, and Primordial Prevention of Rheumatic Diseases

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Abstract

Insights gained during the coronavirus disease 2019 pandemic has underscored the critical role played by both innate and adaptive immune responses in determining the severity of diseases. This newfound understanding holds significant potential to bring about a paradigm shift in the diagnosis, treatment, and management of autoimmune conditions. Advanced technologies that are emerging in the field are expected to play a pivotal role in this transformation. These include the utilization of multi-omics analysis to stratify disease states, the application of precision medicine through the integration of digital technologies, and the implementation of telemedicine to bridge existing regional disparities in healthcare provision.

The objective of this descriptive review is to offer a detailed overview of reclassifying cytokine storm diseases, explore the use of machine learning methodologies in autoimmune diseases, and highlight the importance of incorporating telemedicine and innovative prevention strategies into the management of rheumatoid arthritis. Through this review, we aim to present the most recent research findings and expert insights, and discuss the future prospects and directions in these areas of research.

Keywords: Cytokine storm diseases, machine learning, telemedicine, primordial prevention

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Introduction

The speed and intensity of the antiviral response are critical to the outcome of coronavirus disease 2019 (COVID-19): an early antiviral response with type I interferon (IFN) rapidly reduces viral load, while a reduced antiviral response and its delay increase cytokine/chemokine levels in lung tissue.[1] Reduced virus-specific T cell responses may result in more severe or prolonged viral infection, as the body's immune system fails to elicit an efficacious defense against the pathogen. Such a compromised T cell response can accelerate the clinical decline, with the viral pathogen multiplying more rapidly and inducing greater damage to the host's tissues and organs.[2] As a result, the optimal timing of therapeutic intervention is a subject of debate:[3] Novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection and innate immunity are closely linked, with endosomal viral RNAs being recognized by TLR7/8 and intracellular viral RNAs by RIG-I and MDA5, inducing the production of interleukin-6 (IL-6), tumor necrosis factor (TNF), and type I IFN.[4] However, SARS-CoV-2 infection is also tightly linked to adaptive immunity, where T cells are stimulated by the generation of antibodies against the virus and the presentation of viral antigens by antigen-presenting cells.[5] This excessive immune response results in a cytokine storm, and previous studies have demonstrated the significance of 2 mechanisms: macrophage activation syndrome by IL-1β and a pattern characterized by IL-6-induced immune abnormalities.[6]

Additionally, COVID-19 can cause systemic inflammatory reactions in extrapulmonary organs and an increasing number of immune-related syndromes have been found in COVID-19 patients.[7] There are cases of elevated antinuclear antibodies after serious COVID-19, and the relationship between the pathogenesis of autoimmune diseases and COVID-19 has drawn attention.[8] In other words, the pathogenesis of autoimmune illnesses and COVID-19 share a lot of similarities, and a study on one may have implications for the other.

The diagnosis of autoimmune diseases involves a complex interplay of several factors, including clinical symptoms, medical history, physical examination, laboratory tests, imaging studies, and biopsy. There are many autoimmune diseases, and their diagnosis requires a thorough understanding of their pathophysiology, clinical presentation, and differential diagnosis. Currently, the diagnosis of autoimmune diseases is based primarily on history and physical examination, laboratory tests, and biopsy. The advantage of laboratory tests is that they can detect specific autoantibodies and biomarkers associated with autoimmune diseases and aid in their diagnosis. However, false positives and false negatives can occur, and some tests may not be specific to a particular autoimmune disease. The advantage of biopsy is that it can provide a definitive diagnosis of autoimmune diseases affecting specific organs. However, it is an invasive procedure and may not always be practical.

Machine learning (ML) technology has the potential to significantly enhance the diagnosis of autoimmune diseases by analyzing extensive patient data, recognizing patterns, and providing more precise and personalized diagnoses. However, the application of ML in clinical practice is still in its early stages and requires further validation and testing. The COVID-19 pandemic has forced a widespread shift from in-person care to virtual care through telemedicine. It is suggested that machine learning combined with telemedicine can provide strategies to control outbreaks by providing smart triage and remote monitoring of patients.[9]

This review aims to explain the potential of interdisciplinary research to reclassify cytokine storms and to identify optimal molecular targeted drugs as a technique for personalized medicine that is not limited to a diagnostic name, and it also seeks to present the latest findings of ML as a digital technology in the diagnosis of autoimmune diseases. Finally, we review the difficulties of telemedicine and the primordial prevention of rheumatic diseases.

Interdisciplinary Research to Reclassify Cytokine Storm Diseases and Elucidate Optimal Molecular Targets

A cytokine storm is a phenomenon in which inflammatory cytokines produced by external factors such as infection or internal factors such as an underlying disease are released into the bloodstream in large amounts, triggering an excessive inflammatory response.[10] Large amounts of inflammatory cytokines can cause fatal injuries to different organs, resulting in acute respiratory failure, acute circulatory failure, and even multiorgan failure, which significantly affects the prognosis for life.[11]

The concept became widely known after it was revealed that cytokine storms occur in severe COVID-19 infections.[5,11] The term "cytokine storm disease" refers to a medical condition in which the overproduction of inflammatory cytokines, known as a cytokine storm, is a prominent contributor to the pathogenesis or progression of the disease. These conditions include sepsis, viral infections, lymphoproliferative diseases, autoinflammatory syndromes, autoimmune diseases, and tumor lysis syndromes treated with chimeric antigen receptor (CAR) T cells.[12,13,1415] Table 1 provides a classification of cytokine storm diseases, which can be divided into 5 main categories. The first category is primary cytokine storm syndromes, which include disorders such as hemophagocytic lymphohistiocytosis and macrophage activation syndrome. The second category is secondary cytokine storm syndromes, which can occur as a result of sepsis, viral infections (including COVID-19), and autoimmune diseases. The third category is drug-induced cytokine storm syndromes, which can be caused by treatments such as checkpoint inhibitors and CAR T cell therapy. The fourth category includes inflammatory disorders with cytokine storms, such as acute respiratory distress syndrome and acute liver failure. Finally, hereditary cytokine storm syndromes caused by genetic mutations are included in the last category. Examples of hereditary cytokine storm syndromes include familial Mediterranean fever and TNF receptor-associated periodic syndrome.

Table 1. Classification of Cytokine Storm Diseases

Category	Examples
Primary cytokine storm syndromes	Hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS)
Secondary cytokine storm syndromes	Sepsis, viral infections (including COVID-19), autoimmune diseases
Drug-induced cytokine storm syndromes	Checkpoint inhibitors, CAR T cell therapy
Inflammatory disorders with cytokine storm	Acute respiratory distress syndrome (ARDS), acute liver failure
Hereditary cytokine storm syndromes	Familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS)

ARDS, acute respiratory distress syndrome; FMF, Familial Mediterranean fever; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; TRAPS, TNF receptor-associated periodic syndrome.

Although the idea of cytokine storm has been widely acknowledged since its first report in 1993, the definition of cytokine storm has not been settled.[16] One reason for this may be the diversity of inflammatory cytokines. As a result, immunosuppressive medications are currently utilized to treat cytokine storm disease, though it is unclear which specific cytokine storms each immunosuppressive medication is effective against. For example, tocilizumab, an IL-6 receptor monoclonal antibody, has been developed for the treatment of Castleman's disease, and is effective in that cytokine storm, but it is not clear whether tocilizumab is effective in cytokine storms caused by other factors.[17,18,19]

Thus, cytokine storms differ in the efficacy of therapeutic agents depending on the background disease. As shown in Table 2, there are several important differences between the cytokine storms observed in COVID-19 and those observed in autoimmune diseases. The COVID-19 cytokine storm is thought to be initiated by the activation of pathogen recognition receptors, such as toll-like receptors, by viral RNA and other viral components, leading to the production of inflammatory cytokines such as IL-6, TNF-α, IL-1β.[6,20]

During the early stage of infection, type I IFNs are crucial for controlling viral replication and promoting an antiviral response. However, in severe COVID-19 cases, a delayed and inadequate type I IFN response has been observed, which allows viral replication to continue unchecked. In the late stages of infection, this lack of type I IFN response is compensated by the activation of inflammatory cytokines, including IL-6, IL-1β, and TNF-α, leading to a cytokine storm. This cytokine storm causes widespread inflammation and tissue damage, particularly in the lungs, leading to acute respiratory distress syndrome and multi-organ

Table 2. The Differences between Cytokine Storms in Autoimmune Diseases and COVID-19

Aspect	Cytokine Storm in Autoimmune Diseases	Cytokine Storm in COVID-19
Trigger	Activation of autoreactive T and B cells in response to self-antigens	Activation of pathogen recognition receptors by viral RNA and other viral components
Inflammatory cytokines	Produced by autoreactive T and B cells	Produced by activation of pathogen recognition receptors
Examples of cytokines	IL-17, IL-6, TNF-α, IFN-γ	IL-6, TNF-α, IL-1β
Organs affected	Joints, skin, kidneys (depending on specific disease)	Lungs (mainly), heart, liver, kidneys
Common condition	Rheumatoid arthritis, lupus, psoriasis, multiple sclerosis	COVID-19, a respiratory illness caused by SARS-CoV-2
Efficacy of therapy	Immunomodulatory drugs like corticosteroids, immunosuppressants, and biologics have shown efficacy	Corticosteroids, immunomodulatory drugs, and other antivirals have shown mixed efficacy depending on the disease progression and immune status of the patient.

The manifestation and intensity of cytokine storms can be subject to inter-individual and disease-specific variability. Thus optimal therapeutic and management approaches for cytokine storms should be customized to the individual patient. COVID-19, coronavirus disease 2019; IL-6, interleukin-6; IL-1β, interleukin-1β; IL-17, interleukin-17; IFN-γ, Interferon-γ; SARS-CoV-2, novel severe acute respiratory syndrome-coronavirus-2; TNF-α, tumor necrosis factor-α.

failure. The opposing roles of the early and late stages of type I IFN response underscore the importance of timely and targeted modulation of the immune response in COVID-19 patients to prevent the development of cytokine storm disease.

In autoimmune diseases, the cytokine storm is triggered by the activation of autoreactive T and B cells, which produce inflammatory cytokines in response to self-antigens.[14,21] The organs affected by cytokine storms in COVID-19 are different from those affected by autoimmune diseases. In COVID-19, cytokine storms mainly affects the lungs, causing acute respiratory distress syndrome, but other organs such as the heart, liver, and kidneys can also be affected.[5,11] In autoimmune diseases, cytokine storms can affect multiple organs depending on the specific disease, but most commonly the joints, skin, and kidneys.[14,21] Both COVID-19 and autoimmune diseases involve dysregulation of the immune response leading to cytokine storms, but the triggers, cytokine profiles, and organs affected have important differences.

In situations of sepsis and other infections, tocilizumab suppresses the immune response to the causal microbe as well, raising concerns that this may allow the causative bacterium to thrive. Furthermore, baricitinib and tocilizumab, which are potent suppressors of cytokines, have been used to treat severe COVID-19, but the response to treatment varies from case to case, which may imply that there are differences and diversity in the types of cytokine storms, even in the same disease.[22,23] Although studies have been performed to detect the causes of cytokine storms in individual diseases, there have been few attempts to group and reclassify multiple diseases as cytokine storm diseases and to investigate their treatment. It is challenging to properly differentiate and classify the diversity of cytokine storms, to use effective treatment methods, and to identify the causes of cytokine storms. To improve the prognosis of this severe condition, it is necessary to correctly identify and categorize the variety of cytokine storms and to employ efficient medicines.

One possible way to reclassify cytokine storm diseases is to classify them based on the underlying molecular mechanisms. Traditionally, cytokine storms have been classified based on symptoms and organs involved, but with technologies such as single-cell RNA sequencing and proteomics, we are now able to examine the molecular profiles of individual cells involved in cytokine storm disease. As a result, specific cytokines and pathways underlying cytokine storm disease can be identified, and targeted therapies can be developed to reduce the risk of off-target effects of therapeutic agents. For example, precision medicine can identify specific cytokine receptors or pathways that are over-activated and target them with monoclonal antibodies or small molecule inhibitors.

In summary, the classification of cytokine storms has been refined through the use of molecular profiling techniques that allow the identification of specific molecular mechanisms underlying cytokine storm disease. This information can be used to develop more accurate and effective molecularly targeted therapies for cytokine storm disease.

Application of Machine Learning in the Diagnosis of Autoimmune Diseases

In recent years, there has been a flurry of research aimed at the social implementation of ML in the medical field. Machine learning utilizes algorithms to recognize patterns within data and make predictions.[24] Unlike traditional statistical methods, which aim to establish relationships between specific data based on predefined hypotheses, ML has the capacity to reveal unexpected relationships within data. Furthermore, ML is useful for assessing high-dimensional data, a task that proves challenging for conventional statistical methods. Consequently, ML is applied in clinical research for the analysis of "big data" such as electronic health records, imaging data, biomarker data, genetic data, transcriptome data, and biometric data.

Machine learning involves the construction and application of predictive models such as classification, regression, and clustering. Machine learning is being explored for application in the medical field, including rheumatology, to diagnose, subtype classify, analyze images, forecast prognoses, predict therapy efficacy, and support decision-making for personalized medicine.[24] In rheumatology, including rheumatoid arthritis (RA) and psoriatic arthritis (PsA), several biologics and small molecule molecular targeted therapies are available, but it is difficult to predict which agents will be effective before treatment is introduced. Results of studies aimed at realizing precision medicine via ML analysis using high-dimensional data have recently been published, as described below.

For the application of ML algorithms and model construction, it is essential that the workflow of data preprocessing, model building, and model validation and assessment is properly conducted, which is not easy to do in clinical research. Numerous published research papers in the field of rheumatology have flaws, such

as inadequate sample sizes or a lack of external validation. External validation with large cohort datasets is required to confirm the reproducibility of the model. Additionally, it may be important to develop prediction algorithms for clinical applications of ML by integrating commonly used clinical data and biomarkers.

Machine learning is applied not only for predicting treatment response but also as a diagnostic tool. A recent study introduced an ML-based radiomics approach to distinguish between RA and PsA based on 3 Tesla magnetic resonance imaging (3T MRI) data.[25] In this study, a total of 65 RA patients and 68 PsA patients were used, and radiomics features were extracted from MRI data of the affected joints using ML algorithms. The results showed that the radiomics approach achieved 83.4% accuracy in differentiating RA from PsA, with a sensitivity of 85.5% and specificity of 81.2%. The study concludes that the radiomics approach utilizing ML has the potential to be used as a noninvasive and objective tool for differentiating RA from PsA. The classification criteria for RA demonstrate a sensitivity of 82% and a specificity of 61%.[26] Meanwhile, the classification criteria for PsA, known as the classification for psoriatic arthritis (CASPAR) criteria, exhibit a sensitivity of 91.4% and a specificity of 98.7%.[27] These values are similar to those achieved with radiomics alone. However, it should be noted that these algorithms do not replace clinical judgment and must be used in conjunction with traditional diagnostic criteria and physical examination.

Telemedicine in Rheumatic Diseases

The terms telemedicine and telehealth are often used interchangeably, but they do have subtle differences. Telemedicine typically refers to the remote provision of clinical services, including medical diagnosis and treatment, via electronic communication, such as videoconferencing. On the other hand, telehealth encompasses a broader scope, including not only clinical services but also non-clinical health-related services like health education, administrative meetings, and public health initiatives, all delivered remotely through digital means. In recent years, both mHealth, which uses mobile devices (smartphones, tablets, etc.) to provide health information and services, and eHealth, which uses electronic and information and communication technologies to manage health information and services, have contributed significantly to the advancement of telehealth, including telemedicine.[28] Digital health technology in rheumatic diseases can improve the application of treat-to-target strategies by reflecting patient-reported outcomes in the appropriate timing of face-to-face consultations.[29] However, best practice standards for digital health technology do not yet exist. This paper describes telemedicine as it relates to rheumatic diseases.

Table 3 provides an overview of telemedicine in rheumatic diseases. Telemedicine includes connecting doctors (doctor to doctor: D to D) to offer more specialized medical care to remote areas and connecting doctors to patients (doctor to patient: D to P) to allow remote patients to contact their doctors, with tools for the latter being developed in different technologies. Tools for the latter are a growing market with various technological developments.[30] Before the COVID-19 infection outbreak, telemedicine adoption in the field of rheumatologic collagen disorders was, however, lower than in other sectors, and the clinical value of this technology is still up for debate.[31] In a review article on telemedicine in Latin America, it was noted that during the pandemic, 79% of rheumatologists in Latin America reported using telecommunications, most frequently by telephone and WhatsApp voice messaging. In contrast, 84% reported that telemedicine was appropriate for their patients during the pandemic, but only 54% considered telemedicine to be a valid option for rheumatology care after the pandemic.[32]

A pre-pandemic study of COVID-19 infection reported 2 small randomized controlled trials (RCTs) of telemedicine for rheumatic diseases and found that telemedicine was more accurate and that disease activity and patient satisfaction were not significantly different from face-to-face care.[33] Although telemedicine has the potential to provide immediate care, bridge geographic distances, and make efficient use of limited resources, it has also been reported that many patients with musculoskeletal issues prefer face-to-face interactions with their medical professionals and reject telemedicine.[34] By integrating telemedicine into digital healthcare management, the healthcare industry can not only respond more effectively to the immediate challenges of the COVID-19 pandemic but also lay a foundation for future resilience in facing public health emergencies.[35]

A systematic review examining the efficacy of telemedicine in managing rheumatic diseases, comprising 36 reports on outcomes such as disease activity, quality of life, and patient satisfaction, was conducted through a registered systematic search of interventional or observational studies published between 2015 and 2022. The review found that among the 23 studies utilizing patient satisfaction as an outcome, the majority reported higher patient satisfaction with telemedicine interventions.[36] Additionally, the majority of the intervention studies showed that, although telemedicine's impacts on the key outcomes varied, they were comparable to face-to-face treatment for disease activity control, patient satisfaction, social

Table 3. Overview of Telemedicine in Rheumatologic Collagen Disorders

Content	Details
Overview of telemedicine	– Telemedicine connects doctors (D to D) and doctors to patients (D to P) to provide specialized medical care in remote areas. Tools for D to P telemedicine are evolving with different technologies.
Pre-COVID-19 telemedicine usage and challenges	– Before the COVID-19 pandemic, telemedicine adoption for rheumatologic collagen disorders was lower than in other sectors. The clinical value of telemedicine in this field was debated.
Impact of COVID-19 and increased telemedicine	– The COVID-19 pandemic significantly impacted healthcare, including increased clinical research on telemedicine for rheumatic diseases.
Perspectives on telemedicine use	– A global survey showed 82% of rheumatologists switched to online care during the COVID-19 pandemic, but telemedicine's usefulness for rheumatic patients is debated.
Systematic review of telemedicine efficacy	– A systematic review found that most patients reported higher satisfaction with telemedicine, and its impact on key outcomes was comparable to face-to-face care.
Patient and physician views on telemedicine	– In a 2021 study, over 60% of patients and physicians found telemedicine convenient, but concerns about trust and accurate assessment of results were raised. Many preferred in-person care.

cost, and other patient-reported outcomes.[36] As a result, given that telemedicine for rheumatic diseases may be effective in providing care to patients, randomized clinical trials are required to determine the optimal use of telemedicine in the diagnosis and management of rheumatic diseases.

However, in a report examining the experiences and views of rheumatology patients and physicians regarding telemedicine in 2021 using a questionnaire and in-depth interviews, more than 60% of patients and physicians felt that telemedicine was more convenient. Nevertheless, both patients and physicians had concerns about telemedicine, especially in the areas of building trust and accurately assessing examination results.[37] Telemedicine raised concerns among both patients and physicians, who perceived it as inferior to face-to-face care. According to many patients and physicians, telemedicine leads to misdiagnosis and makes it challenging to provide consistent care. This study showed that in-person care was favored over telemedicine, even though it should be highlighted that it was conducted during a pandemic. It was observed that safe dissemination of telemedicine would require physician training, appropriate patient selection, and reliable consultation with patients and physicians.

Primordial Prevention of Rheumatoid Arthritis

Primordial prevention is a relatively new concept that was initially presented in 1979, focusing on the prevention of risk factor incidence, as reversing established risk factors can be challenging.[38] The ultimate goal in reducing the burden of chronic disease is prevention. Primordial prevention is a social approach, in which changes in the environment subconsciously guide people's behavior and lead to health. Most research on primary prevention has been done in chronic diseases like atherosclerosis.[39] On the other hand, in the field of autoimmune diseases, the focus is on treatment at the time of onset and subsequent secondary prevention, but the evidence is accumulating for the primordial prevention of different autoimmune diseases.[40] This review discusses primordial prevention in RA.

Rheumatoid arthritis is a progressive and destructive disease characterized by anti-citrullinated protein antibodies (ACPA), and the pathogenesis of RA is summarized in an RA-specific multi-step process called the "two-hit model" (Figure 1).[41] Environmental factors such as smoking, periodontal disease, and

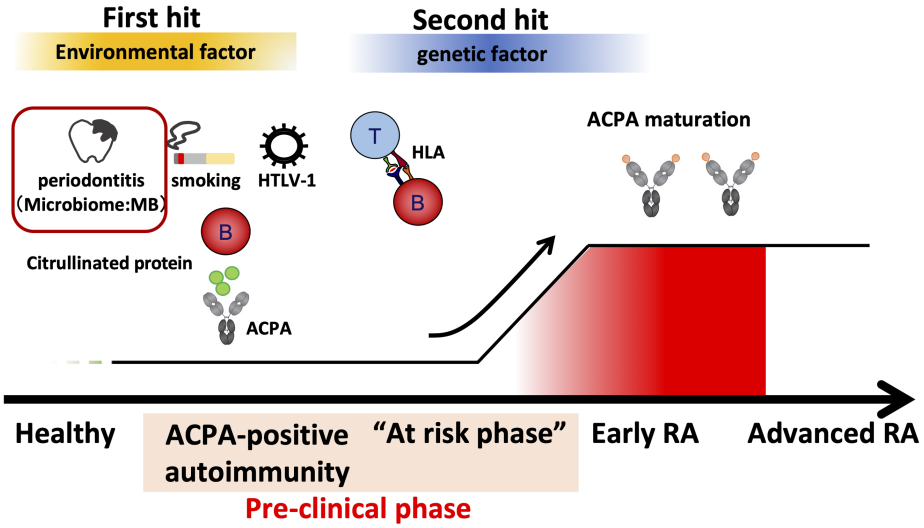

Figure 1. The two-hit model of RA pathogenesis. Environmental factors play a significant role in the development of RA, especially in people with a genetic predisposition. Smoking, obesity, poor oral health, UV exposure, air pollution, and certain foods increase the risk of developing RA. This is known as the "two-hit model," where environmental factors trigger the immune system to produce anti-citrullinated protein antibodies, which can become pathogenic in people with certain genes. Eating a healthy diet, exercising regularly, and avoiding environmental triggers may help reduce the risk of developing RA. ACPA, anti-citrullinated protein antibodies; HLA, human leukocyte antigen; HTLV-1, human T cell leukemia virus-1; RA, rheumatoid arthritis.

abnormalities in the gut microbiome and respiratory microbiome can lead to the destruction of immune tolerance and the synthesis of non-pathogenic ACPA during the "first strike" in individuals.[42] In genetically predisposed populations, a "second hit" renders ACPA virulent. Environmental influences play a significant role in ACPA pathogenesis, accounting for roughly 70% of cases. These include smoking, obesity, social and economic status, UV exposure, air pollutant exposure, dietary factors (salt, seafood, etc.), and sex hormones. Recent studies also implicate the gut microbiome composition and its metabolites, as well as viral infections like human T cell leukemia virus-1 (HTLV-1), and citrullinated proteins, which are generated by the post-translational modification of arginine residues, also contribute to the pathogenesis of RA.[43,44] Proactive health management, including nutrition, exercise, and lifestyle choices, could mitigate environmental impacts and potentially forestall the onset of RA.

The genesis of immune dysregulation in RA is linked to the interplay of immune cells on mucosal surfaces, with oral, respiratory, and gut microbiotas garnering interest as interaction sites. Approximately 80% of early RA patients present with moderate to severe periodontal disease, coupled with altered oral microbiota diversity. *Porphyromonas gingivalis (P. gingivalis)*, a key periodontal pathogen, has a peptidyl arginine deiminase (PAD) that citrullinates human proteins, implicating it in RA pathogenesis. Additionally, anti-*P. gingivalis* antibody titer positively correlates with ACPA levels.[45] *Aggregatibacter actinomycetemcomitans*, another major periodontal pathogen, releases leukotoxin A, which activates PAD in neutrophils, leading to chromatin and citrullinated protein release (neutrophil extracellular traps), which may contribute to ACPA production.[46]

Smoking is a prominent environmental risk factor, contributing to 20-30% of RA cases and is strongly linked to RA development.[47] Prompt smoking cessation is essential for RA prevention, particularly in high-risk individuals, as smoking promotes ACPA formation. However, the impact of smoking on ACPA and rheumatoid factor (RF) levels diminishes over time following cessation, before the clinical onset of RA. Our findings revealed that ACPA positivity was 1.3% in the general population in the Nagasaki Islands Study (NaIS), and the Brinkman Index (BI) value >500 was significantly associated with ACPA positivity (odds ratio (OR) 1.09, 95% confidence interval (CI) 1.02-1.14, or 3.92, 95% CI 1.72-9.22).[43] Additionally, NaIS serum samples predating RA onset were used to examine ACPA glycosylation, its association with HLA-SE, and cross-reactivity of anti-modified protein antibodies in the pre-disease phase.[48,49,50] Moreover, the Nagahama Study identified a correlation between ACPA antibody titers and 3 periodontal disease scores

(missing teeth, community periodontal index, and attachment loss), and in RA patients with severe periodontal disease, ACPA antibody titers were significantly higher in RA patients with severe periodontal disease than in those without severe periodontal disease.[5152]

Conclusion and Future Perspectives

The framework of this review is shown in Figure 2. Cytokine storm disease is a condition characterized by an excessive immunological response that can also occur in infectious diseases such as COVID-19. Currently, cytokine storm disease is being reclassified based on the type of pathogen or immune cell responsible for the disease. It is envisaged that future advancements in techniques and methods will permit a more precise classification. For example, the application of single-cell RNA sequencing technology has been proposed by some researchers to refine the categorization of cell types in cytokine storm syndrome. Additionally, ML could be employed to develop more accurate predictive models. These burgeoning technologies and methodologies are expected to facilitate a more nuanced classification of cytokine storm syndrome, paving the way for optimal therapeutic strategies based on such classifications.

In the future, ML is anticipated to have a growing impact on the diagnosis and treatment of autoimmune disorders. For application in rheumatic diseases, ML-based image analysis technology can automate the determination of synovitis in joint ultrasound and the extent of bone erosion in radiographs. In addition, ML can be used to predict disease progression by analyzing a patients clinical, genomic, RNA, and serum protein information. These technologies can facilitate the development of tailored treatments that are more efficient and effective for patients based on their distinctive genetic and clinical characteristics. Furthermore, ML can support healthcare professionals in making well-informed decisions regarding patient care, enhancing treatment results, and minimizing healthcare expenditures. Nevertheless, it is noteworthy that the application of AI and machine learning in healthcare is still in its nascent stages, and there are several challenges that need to be tackled. These include concerns about the quality and reliability of data utilized for training these algorithms, as well as issues related to privacy and data security. Therefore, it is imperative for healthcare providers and researchers to collaborate in addressing these challenges and ensuring that these technologies are used in a responsible and ethical manner.

In the application of ML to rheumatology, it is essential to promote interdisciplinary collaboration among medical, ML, and information, communication, and technology (ICT) experts. Ensuring data quality and privacy compliance is crucial, as is offering specialized ML training for medical professionals in rheumatology. Encouraging transparent ML models and user-friendly clinical decision support systems can enhance diagnosis and treatment. Establishing a feedback loop for continuous improvement and addressing ethical considerations is important. Patient involvement in ML tool development is recommended for usability. Additionally, disseminating ML research through rheumatology journals, keeping abreast of regulatory updates, and maintaining compliance is vital for the successful integration of ML.

The COVID-19 pandemic has accelerated the adoption of telemedicine for chronic diseases, including rheumatic diseases. Telemedicine enables patients to consult with physicians online from their homes, reducing transportation costs, time, and overall healthcare expenses. In the future, more comprehensive telemedicine is expected to develop, including telemonitoring of rheumatic diseases and telerehabilitation. Nevertheless, there are several obstacles to the implementation of telemedicine for rheumatic diseases. The accuracy of diagnosis and the safety of medical treatment must be ensured. Telemedicine also has limitations, such as the lack of patient-physician communication and the inability to perform physical examinations. To overcome these obstacles, advancements in telemedicine technologies and the creation of disease-specific telemedicine programs are crucial. Additionally, education for both patients and physicians, alongside the promotion of ethical and responsible telemedicine practices, is essential.

The COVID-19 pandemic has brought to light the significance of promoting healthier lifestyles and strengthening the immune system as important public health measures. Similarly, prevention of rheumatic diseases requires the adoption of healthy lifestyle habits, and primordial prevention is expected to play a pivotal role. Primordial prevention aims to prevent the emergence of disease itself by avoiding risk factors. This approach includes improving lifestyle factors, such as physical inactivity, obesity, smoking, and unhealthy diets, which contribute to the development of rheumatic diseases. The pandemic has led to an increase in people staying or working from home, thereby accentuating the importance of healthy lifestyle habits. With more time spent at home, many have had the opportunity to engage in physical activity and prepare healthy meals, reinforcing the need to integrate such behaviors into daily life. Nonetheless, the successful implementation of primordial prevention demands sustained and long-term commitment, as it involves social, cultural, and economic dimensions. To increase public awareness of primordial prevention of rheumatic diseases, educational activities are essential. In the future, tools such as information technology and social media are anticipated to bolster these initiatives.

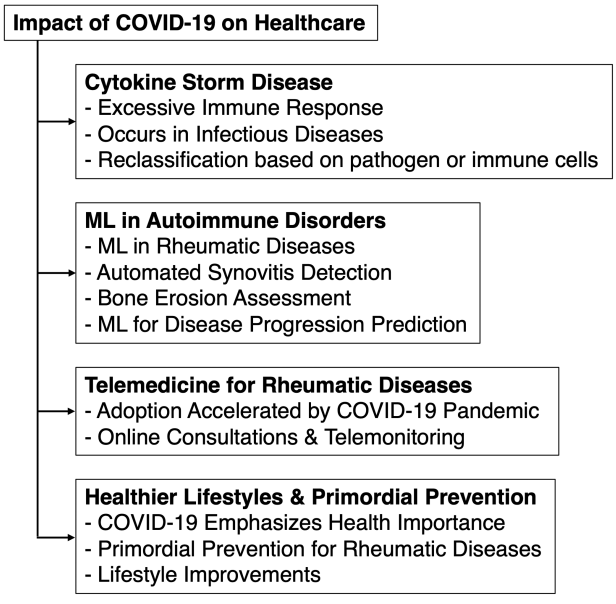

Figure 2. The framework of this review. ML, machine learning.

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