COVID-19 illness and autoimmune diseases: recent insights

Juan Li¹,² · Hong-Hui Liu¹,² · Xiao-Dong Yin¹,² · Cheng-Cheng Li¹,² · Jing Wang¹,²

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Abstract

Background  The aim of this review is to explore whether patients with autoimmune diseases (AIDs) were at high risk of infection during the COVID-19 epidemic and how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic affected immune system.

Methods A systematic literature search was performed using the foreign databases (NCBI, web of science, EBSCO, ELSEVIER ScienceDirect) and Chinese databases (WanFang, CNKI (China National Knowledge Infrastructure), VIP, CBM) to locate all relevant publications (up to January 10, 2021). The search strategies used Medical Search Headings (MeSH) headings and keywords for “COVID-19” or “SARS-CoV-2” or “coronavirus” and “autoimmune disease”.

Results This review evaluates the effect of SARS-CoV-2 on the immune system through ACE-2 receptor binding as the main pathway for cell attachment and invasion. It is speculated that SARS-COV-2 infection can activate lymphocytes and inflammatory response, which may play a role in the clinical onset of AIDs and also patients were treated with immunomodulatory drugs during COVID-19 outbreak. Preliminary studies suggested that the risk of developing severe forms of COVID-19 in patients with AIDs treated with immunomodulators or biologics might not increase. A large number of samples are needed for further verification, leading to an excessive immune response to external stimuli.

Conclusion The relationship between autoimmune diseases and SARS-CoV-2 infection is complex. During the COVID-19 epidemic, individualized interventions for AIDs should be provided such as Internet-based service.

Keywords Autoimmune diseases · AIDs · COVID-19 · SARS-CoV-2

Introduction

A novel coronaviruses (CoVs), called severe acute respiratory syndrome coronavirus-2 (SARS-CoV -2) or coronavirus disease 2019 (COVID-19), was first identified in December 2019 in Wuhan, Hubei Province, China [1]. Due to the relentless spread and pathogenicity of the virus, the World Health Organization (WHO) declared that COVID-19 outbreak have become a global public health concern on March 11th, 2020 [2]. To reduce the spread of deadly the disease and save lives, many countries have introduced emergency containment and control measures including isolate populations, wear a mask and hand sterilization [3]. To date, the number of confirmed reports of new infected persons and deaths is increasing every day across the world. Safe and effective vaccines against COVID-19 pandemic are urgently needed. Notably, COVID-19 vaccines buoy hope. On 11 December 2020, vaccine developed by Pfizer/BioNTech has been given approval for emergency use by the US Food and Drug Administration (FDA) [4]. On 18 December 2020, FDA issued an Emergency Use Authorization (EUA) for the Moderna’s mRNA-1273 vaccine which encodes the prefusion stabilized full-length spike protein of the SARS-CoV-2 [5]. It is necessary to screen contraindication and take precautions before administering COVID-19 vaccines to avoid serious adverse events.

Autoimmune diseases (AIDs) are characterized by generation of autoantibodies, which can activate the complement system and can mediate tissue damage and trigger systemic inflammation [6]. Currently, COVID-19 pandemic has raised concerns about patients affected with...
AIDs. There are two main reasons, one is immunosuppressants are used in the treatment AIDs which may lead to an increased susceptibility to COVID-19 [7]; the other is that the disease itself causes immune dysfunction. Presently, based on the knowledge of other viral infections and the effect of the therapies used in rheumatic patients has led physicians and patients to be concerned that patients with AIDs may be more susceptible to acquiring COVID-19 and may be at greater risk for adverse outcomes [8]. Recently, a comparative cohort study have demonstrated that systemic autoimmune rheumatic diseases patients had significantly higher risks of hospitalization, ICU admission, acute renal failure, and venous thromboembolism versus matched comparators but did not have significantly higher risks of mechanical ventilation or death [9]. Importantly, Caso et al. considered that the shared pathogenetic mechanisms and clinical–radiological aspects between hyperinflammatory diseases and COVID-19 suggest that SARS-CoV-2 may trigger the development of a rapid autoimmune and/or autoinflammatory dysregulation in genetic predisposed individuals, leading to severe interstitial pneumonia [10].

Evidence to date, however, has shown that AIDs patients do not seem to be at an increased risk of infection with SARS-CoV-2 compared with the general population, including in patients treated with immunosuppressant medications [11–13]. Additionally, previous studies have reported the possible antiviral activity of immune-modulating drugs against SARS-CoV-2 including hydroxychloroquine (HCQ), chloroquine (CQ) and tocilizumab—an anti-interleukin (IL)-6 receptor antibody, but there are still controversies [14, 15]. Notably, the symptoms of COVID-19 patients vary from asymptomatic to those with respiratory failure, complicated by ARDS, which may be in part due to an uncontrolled immune-response to SARS-CoV-2 infection triggering a systemic hyperinflammatory response, the so-called "cytokine storm" [16]. These cytokines, including IL-1, IL-6, tumor necrosis factor-α (TNF-α), are released, lead to increased vascular permeability, hemorrhage, and multi-organ failure [17]. More interestingly, one study hypothesized that in the context of SARS-CoV-2 infection, the cause of this transient lymphopenia may be several local inflammatory reaction and release of cytokines, which affect suppression of bone marrow, further, loss of tolerance to self-antigens and, ultimately, autoimmunity [18].

However, the impact of SARS-CoV-2 on AIDs patients remain fully unclear up to now. Thus, based on the available evidence, we will summarize the existing evidence related to the potential role of COVID-19 in AIDs.

**Overview of COVID-19**

**Structure of SARS-CoV-2**

Genomic structure of SARS-CoV-2 similar to that of typical CoVs mainly including an open reading frames (ORFs) polyproteins at the 5′-terminal of the genome of SARS-CoV-2 and four major structural proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins. SARS-CoV-2 uses angiotensin-converting enzyme 2(ACE2) as host cell receptor to entry into cells [19].

**Current status**

As of 10 January 2020, 88,120,981 confirmed COVID-19 cases with 1,914,378 deaths have been reported according to WHO. COVID-19 cases continue to be reported globally from over 220 countries, areas or territories [2]. Notably, with no specific treatment available, as the statistics predict, the mortality and incidence rates of the COVID-19 are rising in global area on each successive day.

**Identification**

Shortly after COVID-19 occur, scientists determined that SARS-CoV-2 was responsible, which is a novel single-stranded RNA virus of the coronaviridae family. To avoid confusion with the recent strain SARS-CoV from 2002, the WHO called the new strain as SARS-COV-2 [2]. To date, by analyzing the whole genome of the pathogen SARS-CoV-2, researchers speculated that the coronavirus may have originated from wild animals (e.g. bat and pangolin), but the identified host is unknown [20]. Mean incubation period was around 6.4 days, ranges from 0 to 24 days [21]. Therefore, contacts were isolated under medical observation for 14 days.

**Symptoms**

The clinical manifestations of COVID-19 are diverse, but respiratory symptoms are often prominent and dry cough, fever and dyspnea are the most common. There can be progression to ARDS with pneumonia and pulmonary fibrosis secondary to a cytokine storm [22]. The elderly and patients with comorbidities such as hypertension and cardiac disease have been shown to be at higher risk [23]. Additionally, laboratory parameters showed COVID-19 patients have high levels of circulating multiple cytokine and/or anti-cytokine, suggesting cytokines may be prominent markers of the pathophysiology of SARS-CoV-2 infection [24].
Transmission

Respiratory droplets and close contact are the main route of transmission [1], thus, public measures such as social distancing and self-isolation can be taken to reduce transmission rates.

Diagnosis

Real-time reverse transcription polymerase chain reaction (rRT-PCR) was used to detect nucleic acid of SARS-CoV-2 in nasopharyngeal, oropharyngeal swab, or the lower respiratory tract samples [25]. Typical computed tomography (CT) findings also have the diagnostic value.

Treatment

A number of COVID-19 vaccine candidates have shown extremely promising results [26], which is expected to be used in the near future. Current treatment strategies of COVID-19 include symptomatic treatment and supportive care (oxygen, mechanical and circulatory support). Various antiviral and other drugs have been used in clinical treatment including HCQ, CQ, azithromycin (AZM), remdesivir, baricitinib and convalescent plasma (CP).

HCQ, CQ, azithromycin (AZM)

To examine risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. Recently, in a cohort study, the result have reported that patients with both AZM and HCQ had increased odds of death than patients with no HCQ or AZM [27]. Furthermore, meta-analysis found that the mortality difference was not significant, neither in HCQ treatment group nor in HCQ plus AZM treatment group in comparison to controls [28]. On the contrary, another retrospective multicenter cohort study have described that there were no significant differences in inhospital mortality between patients who received HCQ with or without azithromycin and patients who received neither drug [29]. However, the interpretation of these findings may be limited by the observational design. Recently, randomized trials were conducted to explore the role of HCQ as a post-exposure therapy for SARS-CoV-2 infection. Results were similar in the HCQ and usual-care groups with respect to the incidence of PCR-confirmed, symptomatic COVID-19. In other words, among persons with recent exposure excluded a clinically meaningful effect of HCQ as post-exposure prophylaxis to prevent SARS-CoV-2 infection. In addition, HCQ also did not reduce the transmission of SARS-CoV-2 or the incidence of seropositivity, and a higher incidence of adverse events (with low severity) in HCQ group than in the control [30, 31]. Notably, a randomized controlled trial (RCT) and a retrospective study have suggested that HCQ did not shorten viral shedding in mild-to-moderate COVID-19 subjects [32]. In brief, HCQ should be used cautiously in the treatment of COVID-19 illness.

Remdesivir, baricitinib

WHO expert groups recommended mortality trials of repurposed antiviral drug—remdesivir in patients hospitalized with COVID-19. Unfortunately, remdesivir had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay [33]. Additionally, three retrospective trials have found that the efficacy of baricitinib, with significant reduction of intensive care unit (ICU) admission, and deaths [34]. An observational, longitudinal trial have reported that baricitinib prevented the progression to a severe, extreme form of the COVID-19 disease by modulating the patients’ immune landscape and that these changes were associated with a safer, more favorable clinical outcome for patients with COVID-19 pneumonia [35]. Drug combination therapy was also concerned. An observational cohort study have found that a combination of baricitinib with corticosteroids was associated with greater improvement in pulmonary function when compared with corticosteroids alone in moderate-to-severe SARS-CoV-2 pneumonia patients [36]. A double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with COVID-19. Combination treatment was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID, especially among those receiving high-flow oxygen or noninvasive ventilation. Serious adverse events were less frequent in the combination group [37]. Collectively, drug–drug interaction and safety concerns should be taken into account before the administration of the recommended drugs.

Convalescent plasma

Due to CP successfully used in other coronaviruses outbreaks and contains neutralizing antibodies against the virus, which may hold promise as treatment for COVID-19. Patients receiving CP transfusion significantly improved the clinical outcomes of COVID-19 patients with diabetes mellitus (DM), especially the cure rate and duration of hospitalization compared with that in COVID-19 patients with DM receiving conventional treatment [38]. Similarly, CP treatment was significantly associated with a higher rate of clinical improvement in moderate and severe cases of SARS-CoV-2 infection and also highlighted administration of CP was a safe treatment option for patients with COVID-19.
illness, with a favorable outcome in the rate and time to clinical improvement [39]. However, there are still many issues to consider, such as the donor selection, indication, administration, and follow-up after transfusion should clearly be defined in national guidelines; interval between COVID-19 symptoms or diagnosis and CP transfusion.

Outcomes

Case fatality rate (CFR) varies geographically. Pooled CFR among confirmed COVID-19 patients was 0.02 (95% CI 0.02, 0.03) [40] (see Fig. 1).

COVID-19 and immune functions

Up till the present moment, the most significant predictors of disease severity relate to either activation or suppression of the host immune response. From this perspective, we will discuss the role of both innate and adaptive immune responses in SARS-CoV-2 infection (see Fig. 2).

Innate immune responses and SARS-CoV-2 infection

Innate immunity is the first defense line to resist the invasion of SARS-CoV-2. When the new virus is able to escape innate immune responses, it can proliferate without hindrance in primarily infected tissues. Subsequently, the tissue associated damage caused by the virus could induce the exaggerated production of proinflammatory cytokines, which the recruitment of proinflammatory macrophages and granulocytes and the generation of immune complexes [41]. In addition, dysregulated production of proinflammatory mediators contributes to ARDS and cytokine storm syndrome, then leading to further tissue damage [42], which may be part of the reason for the relatively high CFR. Reduction in percentages of some innate immune cells may play an important role in COVID-19. For example, the potential association of low eosinophil count and poor prognostic marker in COVID-19 patients was reported [43]. Also, association of COVID-19 severity with proinflammatory cytokines and other immune cell subsets was investigated.

Natural killer

Natural Killer (NK) cells are innate immune responders vital for viral clearance and the control of viral infection [44]. Accumulating researches focused on the immune status of NK cells and the severity of disease in COVID-19 patients. Used single-cell RNA-sequencing on the cells extracted from bronchoalveolar immune cells in patients with COVID-19 (moderate and severe) and healthy controls (HC), Liao et al. reported that bronchoalveolar lavage fluid (BALF) of patients with COVID-19 infection contained significantly higher proportions of NK cells compared to HC, but the proportion of NK cells in patients with severe diseases was decreased than those with moderate infection COVID-19, and NKG2A and CD94 were highly expressed by NK cells [45]. Intriguingly, Demaria et al. suggested that a reduce in NK cell numbers (including absolute numbers and the proportion of mature NK cells) as well as a dysfunctional state of these cells in the blood and lungs of COVID-19 patients than HC, which indicates NK cells do not seem to be associated with the exaggerated inflammatory response observed in ARDS [46]. Similarly, reduced numbers of NK cells in the peripheral blood of COVID-19 patients, which
is associated with severity of the disease and prognosis [47]. Meanwhile, severe COVID-19 patients had significantly lower numbers of circulating NK cells compared with those in mild disease cases and HC, as well as recovering from COVID-19 had higher numbers of NK cells expression than those with active disease [48, 49]. Importantly, further research showed that total number of NK cells was lower markedly and the function of NK cells was exhausted with the increased expression of NKG2A in COVID-19 patients with severe pulmonary inflammation [49]. Additionally, several studies have described that high levels of CD39, CD94, death-ligand 1(PD-L1), and NKG2A (all possibly inhibit the function of T and NK cells) expression were also observed in NK cells isolated from the BALF of ARDS COVID-19 patients [45, 46], suggesting therapies targeting these molecules may contribute to virus elimination by boosting NK cells antiviral immunity at the early stage of SARS-CoV-2 infection. Collectively, these results indicated that due to the loss of NK cells, non-specific immunity is suppressed to a certain extent during COVID-19 infection and it is necessary to early improve NK cells antiviral activity to inhibit the course of the disease progression.

Macrophages

Macrophages are an integral component of innate immunity, which are important for immune response upon injury or infection [50]. Recent researches has revealed to some extent, macrophages may contribute to the disease progression of COVID-19 patients. Park et al. described that ACE2-expressing macrophages contained SARS-CoV-2 nucleoprotein antigen and showed upregulation of IL-6, which may contribute to the excessive inflammation and correlate with disease severity [51]. In mice infected with SARS-CoV-2, the typical histopathology was interstitial pneumonia, especially, alveolar interstitium were filled with infiltration of significant macrophages and lymphocytes, and accumulation of macrophages in alveolar cavities [52]. Remarkably, the viral infection of aggregated alveolar macrophages was obvious from early phase to the late stage in COVID-19 case. In addition, several chemokine and inflammatory cytokines secreted by SARS-CoV-2-infected alveolar macrophages including IL-6, IL-10, TNF-α with specific antibodies and PD-L1 [53]. These observations implied alveolar macrophages might be pivotal in the pathological changes
in COVID-19 patients and macrophages can be a key player of the so-called cytokine storm or macrophage activation syndrome (MAS) by affecting inflammatory monocytic cells, neutrophils and T cell though various chemokines and may be damaging to the tissues [45]. Potential mechanisms were explored the function of macrophages in response to SARS-CoV-2. It is likely that the spike protein (S) of SARS-CoV-2 invades macrophages by binding to ACE2 receptor on the surface of immune cells in lung tissue, thus inducing lung inflammation and injury, indicating the role of abnormally activated macrophages as host cells of SARS-CoV-2 in the pathogenesis of COVID-19 [54]. Besides, coronavirus spike protein induces innate immune response of human monocytes/macrophages by activating NF-κB pathway in vitro [55]. Interestingly, a study observed that few children die from COVID-19 compared to adults in Italy, and then discussed whether macrophages heterogeneity may be important in determining COVID-19 lethality [56]. It is speculated that macrophages populate the important organs including lung in three "developmental waves" and the lungs of children have more macrophages of the first two waves rather than those of the third wave. In other word, different responses to COVID-19 may be related to the number of macrophages in the lungs at the first contact. The molecular mechanisms underlying about different populations of macrophages in COVID-19 disease deserves further study.

Dendritic cells

Dendritic cells (DCs) are professional antigen presenting cells (APCs) that bridges both innate and adaptive immune response [57]. Also, they are potent producers of cytokines that may contribute to immunopathology [58]. Researches reported that associations of specific DC subsets with disease progression in COVID-19 patients. To evaluate the impact of SARS-CoV-2 infection in circulating DCs, using a tSNE tool, specific DCs subsets in the three groups of COVID-19 patients were examined by Sanchez-Cerrillo et al. The finding exhibited CD123hi plasmacytoid DCs (pDC) and CD141 + conventional (cDC) were significantly diminished in the three COVID-19 patient (mild, severe, critical) groups, suggesting a disease-rather than severity-related impact on these cells [59]. Recently, Yang et al. suggested that the SARS-CoV-2-infected DCs in the lungs of COVID-19 patients might be a source of proinflammatory cytokine production that exacerbates the clinical manifestation of COVID-19 [60]. Furthermore, the results showed that attenuated interferon and proinflammatory response to SARS-CoV-2 in human DCs was associated with viral antagonism of STAT1 phosphorylation [60]. In addition, the researchers noted that patients with the same critical condition had different outcomes. Wei et al. displayed that on admission, COVID-19 patients with good prognoses had significantly higher frequency of CD14+ CD11C+ HLA-DR+ subset of dendritic cells compared to those with poor prognoses, suggesting dysregulation of the immune response may affect the outcome of critical COVID-19 patients [61]. These studies increases the knowledge on the role of specific subsets of DCs to SARS-COV-2 infections.

Monocyte

Monocytes are vital effectors and regulators of immune response which stay in the blood for a short time and migrate to inflammatory tissues [62]. In patients with severe SARS-CoV-2 infection, monocytes may play an important role in the pathological process of extensive lung injury caused by cytokine storm. Sanchez-Cerrillo et al. studied the frequencies and activation profiles of monocytes present in the blood of COVID-19 patients with different clinical severity in comparison with healthy individuals and have claimed inflammatory transitional and non-classical monocytes preferentially migrate from blood to lungs in patients with severe COVID-19 [59]. In cohort study, for SARS-CoV-2 PCR-positive patients, low monocyte on admission was found to be associated with severe acute respiratory illness (SARI)/critical disease. COVID-19 patients had higher percentages of monocytes compared with healthy subjects [63]. Significantly reduced non-classical (NC) and intermediate (INT) monocytes were found in acute patients with severe SARS-CoV-2 symptoms, but increased in patients with moderate symptoms NC [64]. Unlike, severe COVID-19 cases had lower levels of monocyte than non-severe ones. More deeply, an observational study noticed that COVID-19 symptomatic patients possessed higher monocyte distribution width mean value than those with paucisymptomatic [65]. Furthermore, an overview of the association of markers in the routine blood test with the severity of COVID-19 have demonstrated that no difference in the monocyte count (weighted mean difference 0.01 × 109/l; 95% CI -0.01 to 0.03) between severe and nonsevere groups [66]. Intriguingly, a review described changes in monocyte function and phenotype that were characteristic of both aging and severe COVID-19, which may explain increased morbidity and mortality of SARS-CoV-2 infection in the elderly [67]. On the other hand, immunological data of children with COVID-19 infection were also reported. Xiong et al. found that children with symptomatic COVID-19 infection had significantly higher monocyte counts [68]. Moreover, the causes of different severity of COVID-19 infection between children and adults can be analyzed in future.

Neutrophil

Neutrophils are the most numerous immune cells. Prior study have showed viruses can also induce neutrophil extracellular
Interestingly, Wang et al. found that neutrophil to CD4+ stratification and a prognostic utility of severe COVID-19. Increased NLR can serve as an early warning signal, risk stratification and as an independent risk factor for adverse the clinical characteristics and death of COVID-19 patients and identified as an independent risk factor for COVID-19 and their correlation with the disease severity have been reported. Severe COVID-19 cases showed significant and sustained increases in neutrophil counts and neutrophil–lymphocyte ratio (NLR) was also higher than mild cases and the older COVID-19 individuals had more chronic diseases and significantly elevated levels of neutrophil compared with the younger patients [73, 74], but among pediatriic patients with COVID-19, moderate cases were associated with a decrease in neutrophil levels than those who with mild clinical characteristics [75]. Additionally, several studies have described elevated NLR was associated with adverse the clinical characteristics and death of COVID-19 patients and identified as an independent risk factor for severe COVID-19 infection [75–77], which suggesting that increased NLR can serve as an early warning signal, risk stratification and a prognostic utility of severe COVID-19. Interestingly, Wang et al. found that neutrophil to CD4+ lymphocyte ratio (NCD4LR) had a better performance than neutrophil to lymphocyte ratio in predicting the virus negative conversion [78]. The possible mechanism of neutrophils in viral infections of SARS-CoV-2 was explored. According to published RNA-seq data sets of lung cells and BALF cells infected with SARS-CoV-2, the results have revealed that infected cells expressed neutrophil-attracting chemokines such as CXCL1, CXCL2, CXCL3 IL-8 and upregulation of neutrophil genes (e.g. MUC21, CXCL1) and chemokines, suggesting likely involvement of neutrophils in COVID-19 lungs [79]. Furthermore, neutrophilia was associated with the development of ARDS and progression from ARDS to death in patients with COVID-19 [22]. On the other hand, the role of NETs in COVID-19 was assessed. Elevated levels of serum NETs in many hospitalized patients with COVID-19 and three markers (cell-free DNA, MPO-DNA, and Cit-H3) commonly used to detect net in blood were measured, and found that all the markers were significantly increased as well as sera from individuals with COVID-19 triggered NET release from control neutrophils in vitro [80]. Barnes et al. have speculated that treatments targeting NETs may reduce the clinical severity and mortality of COVID-19 [81]. In conclusion, these findings highlight neutrophils may be a target for the immunopathologic complications of severely ill COVID-19 patients.

Mast cell

Mast cells (MC) are important sentinel cells for host defense against specific pathogens [82]. There is increasing evidence for the importance of excessive mast cell activation in patients with severe acute as well as chronic ("long haul") COVID-19. Afrin et al. have described that much of COVID-19's hyperinflammation is concordant with manners of inflammation which MC activation can drive and drugs with activity against MCs or their mediators have preliminarily been found to be meaningful in COVID-19 patients. Furthermore, hyperinflammatory cytokine storms may be rooted in an atypical response to SARS-CoV-2 by the dysfunctional MCs of MC activation syndrome (MCAS, usually due to acquired MC clonality) rather than a normal response by normal MCs in many severely symptomatic COVID-19 patients [83]. The potential mechanism may be MC activated by SARS-CoV-2 release histamine which increases IL-1 levels causing cytokine storm and inflammatory reaction in COVID-19, which can amplify the inflammatory process in the lung infected with SARS-CoV-2 [84]. In addition, MCs also communicate with endothelial cells, fibroblasts and macrophages further stimulating release of proinflammatory, fibrotic, thrombogenic and vasoactive mediators [85].

Adaptive immune responses and SARS-CoV-2 infection

Adaptive immune response is mediated by B cells and T cells, which plays a key role against virus [86]. Increasing evidence in characterizing the immune responses, especially adaptive immune responses to COVID-19 infection.

T cell

Recently, T cells including CD4 T and CD8 T play a fundamental role in SARS-CoV-2 infection. Several reports found SARS-CoV-2 infection may affect primarily T lymphocytes and the numbers of both CD4 T and CD8 T cells in moderate and severe COVID-19 cases were markedly decreased [47, 87], in particular, a severe decrease in CD8+ T cells and significantly elevated CD4/CD8 ratio was observed in COVID-19 patients which suggests CD8 T cells may be relevant to the disease severity and mortality of COVID-19 [88]. Strikingly, the clinical manifestations of COVID-19 infection are more consistent with subacute rather than acute viral illness, and this subacute progression pattern increases immunosuppression due to T cell depletion and exhaustion, leading to persistent COVID-19 virus persistence and patient death [89]. The mechanisms of peripheral T cell loss in
B cells are important for the production of antibodies and protective immunity during COVID-19 infection. Recently, epidemiological studies have focused on the expression of B cells in patients with virus infection. Lymphocyte subsets count including B cell (CD19 +) were significant reduction in patients with severe/critical COVID-19 disease compared to mild/moderate disease [94]. A significant decrease of B cell is positively correlated with in-hospital death and severity of illness [95]. Measure/monitor the response of B cells to understand how the immune system responds to this harmful virus. Schultheiß et al. explored that the B cell response to SARS-CoV-2 in convalescent patients may last only a few months [99]. Various, S-specific antibodies, memory B cells and circulating follicular helper T cells were found in the plasma of convalescent patients with COVID-19, but the median value of blocking the interaction between ACE2 and virus binding site was weak (about 14%) in immune plasma of patients [100]. These results indicated that the role of immune system and SARS-CoV-2 infection in human body is complex, which needs to be further verified by large samples.

**SARS-CoV-2 and autoimmune diseases**

A better understanding of the implications of COVID-19 in AIDs patients is urgently needed to guide clinicians in the caring for patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), type 1 diabetes (TID), systemic sclerosis (SSc), ankylosing spondylitis (AS) and psoriasis (See Table 1).

**Rheumatoid arthritis**

RA, a chronic systemic autoimmune disease, is characterized by synovial joint inflammation [101]. There is great interest in understanding the outcomes of COVID-19 in RA patients, or whether it makes them more prone to rapidly progress into severe COVID-19. Schett et al. analyzed that the pattern of proinflammatory cytokines induced in COVID-19 has similarities to those targeted in the treatment of rheumatoid arthritis, but preliminary data from high-risk areas suggested that there is no an increased risk of COVID-19 in patients with inflammatory arthritis [102]. Previous study suggested that ambient respiratory viral infections including coronavirus in the population were associated with an increased number of incident RA. Similarly, a nationwide retrospective case–control study found that RA [odds ratio
| AIDs (e.g., RA, SLE, SSc) | Study [ref] | Country | Date (Mo. day) | Patients N (female %) | Age(year) | COVID-19 (N) | Symptoms | Treatment (baseline) | Outcomes |
|---------------------------|-------------|---------|----------------|----------------------|-----------|-------------|----------|---------------------|----------|
| AIDs D’Silva 2020 [8]    | USA         | Jan 20–Aug 15 | 2379 (79%) | 57±16 | AIDs 2379 (Positive) | VS without AIDs 2379 (Positive) | B-cell activating factor inhibitor, CTLA-4 immunoglobulin, IL-1/IL-6 receptor/IL-17/IL-23/JAK/TNF/CD20 inhibitor | SARD patients VS non-SARD comparators: hospitalization (RR 1.14, 95% CI: 1.03–1.26), ICU admission (RR 1.32, 95% CI 1.03–1.68), ARF (RR 1.81, 95% CI 1.07–3.07) |
| AIDs (e.g., SLE, SSc, RA) | Emmi 2020 [10] | Italy | April 1–14 | 458 (74%) | 56(43–68) | 1 (Positive) | Fever, fatigue, cough, dyspnea | Corticosteroids, colchicine, mycophenolate, HCQ, biologic DMARDs, TNF-α inhibitors, tocilizumab | AIDs 0.22% (95%CI 0.01–1.21%) VS general population 0.20% (95% CI 0.20–0.21%) |
| AIDs (SLE, AAV, SSc, RA, IIM) | Zen [11] | Italy | April 9–25 | 916 (78.6%) | 53.6 ± 14.3 | 2 (Positive) | Fever, cough, sore throat, arthralgias, diarrhea, ageusia/hyposmia, conjunctivitis | Prednisone, anti-BLYSS Ethotrexate, anti-CD20, cyclosporin, CTLA4-lg, mycophenolate, JAK-i, tacrolimus, azathioprine, cyclophosphamide, anti-IL6R, antimalarial, leflunomide, anti-TNF, salazopyrin | The incidence of SARS-CoV-2 infection was low and seems to be comparable to that of the general population |
| SLE | Pablos 2020 [109] | Spain | – | 2253 (77%) | 51 (42–66) | 1397 (Positive) | – | COVID-19 prevalence % (CI in SLE patients is 0.62 (0.34–1.04); The prevalence of COVID-19 in SLE patients is similar to the reference population [1.07 (0.63–1.80)]) |
Table 1 (continued)

| AIDs   | Study [ref] | Country   | Date (Mo. day) | Patients N (female %) | Age(year) | COVID-19 N (N) | Symptoms | Treatment (baseline) | Outcomes                                                                 |
|--------|-------------|-----------|----------------|-----------------------|-----------|----------------|----------|----------------------|--------------------------------------------------------------------------|
| SLE    | Fernandez-Ruiz 2020 [110] | USA       | April 13–June 1 | 226 (92.9%)           | –         | 41 (Positive)  | fever, cough, sore throat, diarrhea, loss of taste/smell, shortness of breath | HCQ, systemic steroids, NSAIDs, Mycophenolate Mofetil, Methotrexate, Azathioprine, Belimumab, Cyclophosphamide, Rituximab, Abatacept, Tocilizumab | SLE patients with confirmed COVID-19 have a high rate of hospitalization but a similar mortality rate to the general population; Non-white race, BMI, and the presence of one or more comorbidities were identified as independent predictors of hospitalization in SLE patients who develop COVID-19, similar to the general population |
| RA     | Ji 2020 [101] | Korea     | Until May 15    | 219,961 (47.4%)       | –         | 7341 (Positive) | –        | –                   | RA was associated with an increased risk of severe COVID-19 (ORR 1.207–1.244) |
| MS     | Castillo 2020 [118] | Spain     | –              | 300 (75%)            | 47.91 (22–74) | 9 (Positive)   | Fever, cough, sore throat, arthromyalgias, loss of smell, shortness of breath | –                          | COVID-19 is twice as common in people with MS as in the general population (OR 2.67; IC 95% 0.37–19.07), but there was not statistically significant |
| MS     | Louapre 2020 [119] | French    | March 1–May 21  | 348 (71.8%)           | 44.6 ± 12.8 | 146 (Positive) | Fever, digestive disorders, asthenia/ageusia, headache, cough, asthenia, dyspnea, dizziness, dyspnea | IFNβ, Glatiramer, teriflunomide, dimethylfumarate,natalizumab, fingolimod, ocrelizumab, rituximab, cladribine, alemtuzumab | EDSS ≥ 6 (OR 6.3, 95% CI 2.8–14.4) was independent risk factors for a COVID-19 severity score of 3 or more (indicating hospitalization or higher severity) |
| IBD    | Aziz 2020 [130] | USA       | until May 13    | 9177 (99.2%)          | –         | 32 (Positive)  | –        | Steroids, biologics, aminosalicylates, immunomodulators | 32 were reported to have confirmed COVID-19 (0.3%, 95% CI, 0.1%-0.5%) |
| AIDs  | Study [ref] | Country | Date (Mo. day) | Patients N (female %) | Age(year) | COVID-19 (N) | Symptoms | Treatment (baseline) | Outcomes |
|-------|------------|---------|----------------|-----------------------|-----------|-------------|----------|---------------------|----------|
| IBD   | Axelrad 2020 [136] | USA | March 3–May 10 | 83 (47%) | 35 (27–45) | 45 (Positive) | Fever, cough, pharyngitis, rhinorrhea, ageusia, diarrhea, anosmia, shortness of breath | Azathioprine/Mercaptopurine, Anti-TNF, Methotrexate, Prednisone, Oral budesonide, Vedolizumab, Ustekinumab, Tofacitinib, 5-ASA, | In IBD patients, severe outcomes of COVID-19 were rare and comparable to similarly aged individuals in the general population and generally limited to older men with comorbidities and/or patients with active CD |
| IBD   | Singh 2020 [135] | USA | Jan 20–May 26 | 196,403 – IBD: 232 (Positive) VS non-IBD: 19,776 (Positive) | – | Fever, dyspnea, cough, sore throat, nausea/vomiting, malaise/fatigue, diarrhea, abdominal pain, hypoxemia | Biologics and/or immunomodulators, aminosalicylate, corticosteroids | The risk of severe COVID-19 was similar (RR 0.93, 95% CI 0.68–1.27, P = 0.66); IBD patients with severe COVID-19 were older and had a higher proportion of multiple comorbidities |
| IBD   | Gubatan 2020 [134] | USA | March 04–April 14 | 168(52.4%) | 47.7 ± 16.3 | 5 (Positive) | Fever, dyspnea, cough, sore throat, fatigue, body pain, pneumonia, diarrhea, abdominal pain, nausea /vomiting, nasal congestion, | ACE Inhibitor,ARB,PPI, H2 blocker,Methotrexate,6MP/Azathioprine,5-ASA, Anti-TNF agent, Vedolizumab,steroids, NSAIDs Ustekinumab, Antiplatelets, Anticoagulant | The prevalence of COVID-19 was 3.0%; IBD patients with COVID-19 were older, more obese, more likely to have hypertension and DM; Age > 66 years was independently associated with increased risk (OR 21.30, P = 0.022) of COVID-19 |
range (ORR), 1.207–1.244] showed significant association with risk of infection of COVID-19 [103]. A potential link between COVID-19 infections and the development of RA needs to be studied further. Interestingly, during COVID-19 epidemic, the implementation of a telemedicine programme for patients with RA in a few countries to reduce cross infection [104]. Rheumatoid Arthritis Impact of Disease (RAID) score could help identify the RA patients who are best suited to a telemedicine consultation as well as follow-up, and could also promote holistic management of subjective symptoms that might otherwise be overlooked [105]. However, whether telemedicine can effectively control the disease activity of RA and provide the best treatment is still questionable [106, 107]. In our opinion, first, it is important to assess the patient’s willingness to receive a telemedicine. Second, several digital applications for monitoring disease activity should use and the risk of infection can be classified according to the treatment plan, age and complications of RA patients to make telemedicine even more reliable and improve efficiency and quality of healthcare assistance.

**Systemic lupus erythematosus**

SLE is an autoimmune disease with the production of autoantibodies against self-antigens and loss of immunological tolerance which causes tissue and organ damage [108]. Since the COVID-19 pandemic, whether SLE patients have a high risk of serious diseases has been widely concerned. Several studies speculated that SLE infection does not seem to increase the risk of SARS-CoV-2 [109, 110]. Also, Pablos et al. found that patients with SLE did not significantly increase the prevalence of PCR+ COVID-19 in hospitals [111], while Fernandez-Ruiz et al. have found that SLE patients with confirmed COVID-19 have a high rate of hospitalization but a similar mortality rate to the general population [112]. For SLE patients under immunosuppressive treatment, Gendebien et al. showed that there was not significant a higher rate of COVID-19 infection or symptoms [113]. Whereas, Wallace et al. have inferred that SLE patients may develop more severe manifestations of COVID-19 infection, even relative to patients with other AIDs [114], which may be due to the higher rate of black race, respiratory comorbidities, glucocorticoids and tobacco exposure in SLE patients. Noteworthy, from a novel perspective, a study found that epigenetic dysregulation could lead to an increased risk and severity of SARS-CoV-2 infection in patients with lupus, regardless of the concomitant immunosuppressive medications. Moreover, in lupus patients, ACE2 gene is demethylated and overexpressed, which encodes the receptor for SARS-CoV-2 spike glycoprotein, facilitating viral entry and enhancing viraemia [115]. Additionally, whether patients with SLE who have been treated with CQ, HCQ or others are infected with COVID-19. Konig et al. concluded that

| Table 1 (continued) | AIDs | Study [ref] | Country | Date (Mo. day) | Patients N | N (female %) | Age(year) | COVID-19 (N) | Symptoms | Treatment (baseline) | Outcomes |
|---------------------|------|-------------|---------|---------------|------------|-------------|-----------|-------------|----------|---------------------|----------|
| T1D                 | Vangoitenhoven [144] | Belgium | Feb 1–April 30 | 2,336(48.5%) | – 4 (Positive) | – | – | – | – | People with T1D did not have an increased risk of worse COVID-19 outcomes (hospitalization or mortality); T1D patients who were hospitalized were older than those who were not hospitalized, but no significant in terms of glucose control or comorbidity profile. |
| IMID                | – | – | – | – | – | – | – | – | – | – | – |
| SLE                 | – | – | – | – | – | – | – | – | – | – | – |
| DMARDs              | – | – | – | – | – | – | – | – | – | – | – |
| ANCA                | – | – | – | – | – | – | – | – | – | – | – |
| SSc                 | – | – | – | – | – | – | – | – | – | – | – |
| RA                  | – | – | – | – | – | – | – | – | – | – | – |
| IIM                 | – | – | – | – | – | – | – | – | – | – | – |
| EDSS                | – | – | – | – | – | – | – | – | – | – | – |
| CI                  | – | – | – | – | – | – | – | – | – | – | – |
| DM                  | – | – | – | – | – | – | – | – | – | – | – |
| CD                  | – | – | – | – | – | – | – | – | – | – | – |
| SARDs               | – | – | – | – | – | – | – | – | – | – | – |
| ARF                 | – | – | – | – | – | – | – | – | – | – | – |
| ICU                 | – | – | – | – | – | – | – | – | – | – | – |

**AIDs** autoinflammatory disease, **DMARDs** disease-modifying anti-rheumatic drugs, **ANCA** antineutrophil cytoplasmic antibodies, **IL** Interleukin, **RA** rheumatoid arthritis, **ARD** autoimmune rheumatic disease, **ACE** angiotensin-converting–enzyme, **ARB** angiotensin II receptor blocker, **IL** interleukin.
patients with SLE on baseline therapy with HCQ are not universally protected from COVID-19 [116]. Similarly, preliminary findings suggested that although most of the SLE patients received long-term treatment with HCQ and blood concentrations of the drug within therapeutic range, HCQ did not seem to prevent COVID-19, at least its severe forms, in patients with SLE [117]. Given interfering with coronavirus replication in vitro, the increased bioavailability of type 1 IFN in SLE possibly promotes host defenses against COVID-19 infection and adjunct therapy [118]. In summary, on the premise of taking measures to prevent SARS-CoV-2 infection, SLE patients should continue to receive reasonable treatment and many susceptible factors and comorbidities should be taken into account, which may prevent the serious complications related to COVID-19. A larger cohort of SLE patients, infected with SARS-CoV-2 is required to better understand the impact of COVID-19 on SLE patients and evaluate the clinical efficacy of these drugs (both antiviral and immunomodulatory).

Multiple sclerosis

MS is a chronic inflammatory, demyelinating neurodegenerative disease of the central nervous system (CNS) [119]. With the continuous spread of COVID-19, it is very important to evaluate the relationship between MS and COVID-19 and take appropriate protective measures in time. Castillo et al. have reported that COVID-19 is twice as common in people with MS as in the general population (OR 2.67; IC 95% 0.37–19.07), but there was not statistically significant [120]. Additionally, Louapre et al. have described Expanded Disability Severity Scale score (EDSS) ≥ 6 (OR 6.3, 95%CI 2.8–14.4) was independent risk factors for a COVID-19 severity score of 3 or more (indicating hospitalization or higher severity) [121]. Results from registry-based cohort showed that patients with MS was independent risk factors for severe COVID-19, while no association found between disease-modifying therapies (DMTs) exposure and COVID-19 severity [121]. Likewise, derived from a small sample size, the frequency measure of COVID-19 in patients with MS living in the Veneto region seems to be 2.5 times higher than general population, but DMT exposure did not seem to be associated with a high risk of COVID-19 or its complications, even in some cases of immunosuppression [122]. Furthermore, in the largest cohort study, death from COVID-19 was strongly associated with chronic neurological conditions including MS [123]. Interestingly, according to the formula, Cristiano et al. analyzed that these estimates would represent that every 21,163 cases of COVID-19, there could be expected one patient with MS infected in Argentina [124]. However, Fan et al. reported that there was no increased risk of COVID-19 infection was observed in patients with MS or neuromyelitis optica spectrum disorders (NMOSD) [125].

The possible reason is that a variety of stringent measures that have been taken to protect MS patients against risk of COVID-19 infection. The impact of immunosuppressive drugs used in the treatment of MS on COVID-19 severity was also explored. According to Italian Society of Neurology (ISN) and the Association of British Neurologists (ABN), both consider safe to start or continue treatment with first line (e.g. IFN-β, teriflunomide) and non-lymphodepleting second line DMTs such as fingolimod and natalizumab. For example, a case of COVID-19 in a patient with MS treated with natalizumab, with excellent recovery and repeated negative results in five consecutive microbiological studies, which may be due to the blockade of integrins induced by natalizumab [126]. It was a reasonable speculation that immune reconstitution induced by treatment may induce positive changes in the immune system in the defense against COVID-19. As for lymphodepleting DMTs (alemtuzumab, ocrelizumab, rituximab or cladribine), individual factors such as disease activity and lymphocyte count should be taken into account, but a temporary delay in initiation or administration is generally recommended (between 6 and 12 months) [127]. For instance, anti-CD20 monoclonal antibodies like rituximab or ocrelizumab increase the susceptibility of MS patients to SARS-CoV-2 infection[128], while several researches proposed that anti-CD20 monoclonal antibodies may have protective role against COVID-19 disease [129, 130]. Notably, these data were considered only preliminary, the effect of COVID-19 on MS should be interpreted cautiously. Further work is needed to provide the rationale for strategies regarding clinical management of patients with MS during the COVID-19 pandemic.

Inflammatory bowel disease

IBD, including ulcerative colitis (UC) and Crohn’s disease (CD), are characterized by progressive and relapsing dysfunction of the gastrointestinal tract [131]. As the COVID-19 rapidly spread, both physicians and patients have been deeply concerned about the possible increased risk of COVID-19 infection in patients with IBD. In a study of 9177 IBD patients in USA, 32 were reported to have confirmed COVID-19 (0.3%, 95% CI 0.1–0.5%) [132]. Despite a few studies found that patients with IBD more likely to be affected by the COVID-19 pandemic [133, 134]. Fortunately, overall available evidence suggests that IBD patients, even patients treated with medication, might have no increased risk of developing COVID-19 [135, 136], suggesting medical therapy with immunomodulators or biologics may not increases the risk of this infection. Also, information regarding the characteristics and prognosis of SARS-CoV-2 infection in patients with IBD was required. Patients with IBD and a positive test for SARS-CoV-2 have a good overall prognosis and severe outcomes of COVID-19 were rare
and comparable to similarly aged individuals in the general population [137, 138]. New-onset diarrhea and abdominal pain were significantly more frequent in IBD patients with COVID-19 than without, which highlights the need for COVID-19 evaluation in IBD patients with new gastrointestinal symptoms [139]. More importantly, factors determining susceptibility to COVID-19 in IBD patients were identified. Krzysztof et al. analyzed that age, smoking, the presence of inflammation and anatomical location were key determinants which effect expression of virus receptor ACE2 and TMPRSS2 in IBD patients [140]. In addition, SARS-CoV-2 was detected in fecal samples from patients with COVID-19, and high concentrations of ACE2 were found in the inflamed intestinal ileum and colon of IBD patients. The results may provide a possible mechanistic link. Based on the emerging evidence and high risk factors, such as age, disease activity, drug therapies and comorbidities were also considered, many expert have proposed that specific guidelines and recommendations (such as use of immunomodulatory drugs and protection of daily life) for IBD patients including adults and children in the current pandemic era to assure the safety of ongoing treatment and adjust individualized care [141–143]. It should be noted that the adoption of these recommendations should take into account the occurrence of local COVID-19 and combine with local guidelines and isolation measures to seek the optimal solution. During the epidemic period of the SARS-CoV-2, to improve the communication between doctors and patients, and to provide specific suggestions for IBD patients, some alternative solutions have been implemented, including restrictions on infusion devices, telmedicine, online drug delivery services and patient education on measures to prevent infection [144].

Other autoimmune diseases

TID, also known as insulin-dependent diabetes mellitus, an autoimmune disorder, is usually diagnosed with insulin deficiency [145]. Data regarding potential effects of SARS-CoV-2 infection on patients with T1D are emerging. Vangoitsenhoven et al. have showed that community-dwelling people with T1D did not have an increased risk of worse COVID-19 outcomes defined as hospitalization for COVID-19 or mortality [146]. To evaluate the impact of lockdown on glucose control in T1D patients, Capaldo et al. found that adults with T1D had improved glucose control indicated by increased time in target range, reduced glucose variability, and reduced hyperglycemia and severe hypoglycemia, indicating the importance of a more stable rhythm of life, including more regular mealtimes [147]. Further, using a hybrid closed loop (HCL) system, Torinese et al. showed that the glycemic control of T1D in adolescents did not worsen during the restrictions due to COVID-19 pandemics and further improved in those who continued physical activity (PA) during the quarantine [148]. Patient characteristics and adverse outcomes among patients with T1D diabetes with confirmed COVID-19 was also explored. Patients were classified as COVID-19-positive case group and COVID-19-like case group, the most prevalent adverse outcome was diabetic ketoacidosis (DKA) and high blood glucose in both groups [149].

SSc is an autoimmune disease characterised by fibrosis of the skin and internal organs and vasculopathy [150]. Because interstitial lung disease (ILD) is a common complication seen in patients with SSc, there has been concern that patients with SSc may be at increased risk for acquiring COVID-19 and/or at increased risk for adverse outcomes. To date, however, this has not been demonstrated. The World Scleroderma Foundation have provided answers to the main practical questions for physicians and SSc patients (Up to date 14 April 2020) and Minniti et al. have proposed preliminary advice on how to take care of these patients during the COVID-19 pandemic [151, 152]. For example, patients should continue immunosuppression to avoid SSc relapses and stopping or reducing therapy should be agreed with physician. When family members or themselves are infected, immunosuppressive drug interruption may be advised. There is no evidence to support that SSc patients benefit from additional supportive/preventive therapy including prophylactic use of drugs and adjunctive therapy. Telemedicine consultations and assessments are encouraged. For severe SSc-COVID-19-infected patients, antiviral therapy or tocilizumab may be a rescue treatment to avoid ARDS. The routinely use of corticosteroids for treatment of viral pneumonia is not recommended and should be carefully employed in SSc. Drug-induced immunosuppression and risk of SARS-CoV-2 infection were explored in SSc patients. Patients with systemic sclerosis treated with rituximab might not exhibit an increased risk of severe COVID-19 and a careful follow-up is required, because these patients may experience a delayed progression [153].

AS is a chronic inflammatory disease, characterized by the enthesis of sacroiliac joints and the spine [154]. To date, little is known with regard to the effect of COVID-19 among patients with AS. A 61-year-old patient with AS who presented with gastrointestinal symptoms, newly onset fever and respiratory manifestations following the admission, then, RT-PCR test for SARS-CoV-2 resulted positive. Substantial clinical improvement was achieved with HCQ, prednisolone, tocilizumab and enoxaparin sodium [155]. Another case reported that a COVID-19 patient with AS treated with etanercept had olfactory and gustatory sensory dysfunction [156]. More studies are warranted to analyze clinical characteristics and outcome of COVID-19 patients with AS on immunosuppressive agents.

Psoriasis is a common chronic and recurrent inflammatory skin disease [157]. The prevalence of COVID-19
in psoriasis/autoimmune skin diseases patients was 0.011 (95% CI 0.006–0.021), and the mortality due to COVID-19 in patients with psoriasis/autoimmune skin diseases was 0.097 (95% CI 0.042–0.21) [158]. A single-center case–control study have suggested that psoriasis patients on biologics displayed higher risk to be infected and to be hospitalized/self-quarantined at home, but ICU hospitalization and death did not differ from the general population. Besides, comorbidities associated with psoriasis (such as hypertension, obesity, and diabetes) worsen the outcome of COVID-19 illness [159]. It is worth exploring whether immunosuppression or immunoregulation makes psoriasis patients receiving biotherapies more susceptible to COVID-19 infection. Using randomized clinical trials (compared overall infection rates, rates of upper respiratory infections and nasopharyngitis), Lebwohl et al. have found that the rates of nasopharyngitis and upper respiratory tract infections are similar to placebo [160]. Similarly, compared to the general population, there is no increased susceptibility for SARS-CoV-2 infection or increased severity of the disease course of COVID-19 in patients with psoriasis receiving systemic treatments, including biologics [161]. These studies suggested that biological therapy should be continued in patients with immune-mediated skin diseases during the COVID-19 outbreak. More importantly, dermatologists should provide best advice on the treatment of cutaneous immune-mediated diseases during the COVID-19 pandemic on an individual basis.

Effects of treatment for AIDs on SARS-CoV-2 infection

Understanding the impact of immunosuppressive therapy on the progression of COVID-19 in patients with AIDs can guide the physician to achieve an effective protective strategy or, when infected, to optimise a real-time treatment. Patients were divided into two groups based on whether they are taking or not taking biologics (e.g. TNF inhibitors, IL-6 inhibitors, kinase inhibitors, etc), the results have showed that the group on immunosuppressive drugs had significantly lower odds of hospitalizations and ICU admissions compared with the other group, but the risk of COVID-19 illness remains the same between the study groups [162]. Similarly, COVID-19 is more frequent in the subgroup of autoimmune systemic diseases patients without ongoing conventional synthetic disease-modifying anti-rheumatic drugs (HCQ and methotrexate) [163]. Case series of individuals with 600 rheumatic disease patients from 40 countries have demonstrated that biologic therapies and non-steroidal anti-inflammatory drug (NSAID) were not associated with a higher risk of hospitalisation for COVID-19, but anti-TNF with a decreased odds of hospitalisation in patients with rheumatic disease [164]. Interestingly, some hypotheses may explain why a higher incidence of fatal COVID-19 outcomes was not found in AIDs patients on systemic treatments. Patients with AIDs under systemic treatment may pay more attention to personal protection (e.g., hand disinfect, wearing a facial mask, social distancing) compared to the general population. Another hypothesis is that a possible protective effect against harmful manifestations of COVID-19 provided by biologics. Inhibition of the COVID-19 immune response would be harmful in the early phase of infection, but it would be helpful in the progression to the severe form of the disease [163]. Additionally, previous studies of coronavirus have shown adverse reactions including delayed virus clearance and potential complications in patients receiving high doses of corticosteroids [165, 166], thus, in the absence of controlled clinical trials on the use of corticosteroids, on September 2, guidance from WHO advises against the use of corticosteroids patients with nonsevere cases, but systemic corticosteroids were recommended for the treatment of severe and critical patients with COVID-19 [167]. Huang et al. have found that patients with corticosteroids use have significantly worse clinical outcomes including ARDS, shock, kidney injury, continuous renal replacement, secondary infection than patients who did not receive corticosteroids [1]. Meta-analyses of observational studies have concluded that glucocorticoid use increases the risk of SARS-CoV-2 infection and might contribute to the higher prevalence of COVID-19 in ADs [158]. Should the immunosuppressive treatment be stopped in AIDs patients during the pandemic? On balance, it is advisable that AIDs patients continue treatment [168, 169]. A reasonable explanation is that discontinuation of the use of biological increase the risk of flares of the underlying autoimmune condition, which itself is an increased risk factor for infections [170]. Notably, the treatment plan should comprehensively take into account the characteristics of individual patients, such as age, gender, complications and disease condition [159]. AIDs patients on biologics should be carefully monitored with telemedicine during COVID-19 outbreak and early treated. Several studies have evaluated the impact of anti-CD20 agents on immune response to vaccines. Humoral vaccine responses were significantly impaired by B cell depleting anti-CD20 monoclonal antibody therapies, particularly to a neoantigen [171, 172]. From published rituximab and unpublished ocrelizumab (NCT00676715, NCT02545868) trial data, protective neutralizing antibody and vaccination responses are predicted to be blunted in CD-20 treated people until naïve B cell repopulate, based on B-cell repopulation-kinetics and vaccination responses [173]. Due to vaccinations against SARS-COV-2 will begin in the near future, for patients already on anti-CD20 therapy, this may not make sense, since the immunosuppressive effects of these agents are long-lasting (usually greater than 6 months), but for patients currently considering anti-CD20 treatment, especially those whose
overall survival is not improved by anti-CD20 treatment, physicians should carefully weigh the risk/benefit ratio of anti-CD20 treatment [172]. Additional longitudinal studies are needed to confirm these findings.

**Conclusion and future challenges**

Understanding the risk of acquiring COVID-19 in patients with AIDs remains critical, as does decision-making regarding management of immune modulatory therapy in this patient population during the pandemic. The relationship between autoimmune diseases and SARS-CoV-2 infection is complex. We have explored that the effect of SARS-CoV-2 on the immune system through ACE-2 receptor binding as the main pathway for cell attachment and invasion, also known as cytokine storm, which is characterized by hyper-activation of T cells and massive production of several cytokines. SARS-CoV-2 infection can activate lymphocytes and inflammatory response, which may play a role in the clinical onset of AIDs disease and patients treated with immunomodulatory drugs during COVID-19 outbreak. Thus, it may be a reasonable speculation this pathogen may be associated with either the triggering or the exacerbation of AIDs disease. However, based on the current literature, preliminary data suggested that the real risk of developing severe forms of COVID-19 in patients with AIDs treated with immunomodulators or biologics might not increase. Notably, some experts have given recommendations and guidelines based on risk stratification and local epidemic prevention measures to guide clinicians in the care of patients. During the COVID-19 epidemic, the new management strategy for AIDs patients was used such as internet-based service to provide an individualized approach of AIDs interventions.

There are still several questions that remain unknown. For instance, the potential infectious risk of stool samples and human intestinal tract may serve as an alternative infection route for SARS-CoV-2. Moreover, does the presence of some clinical symptoms of AIDs, such as intestinal inflammation and fibrosis, can affect the clinical course of COVID-19? Is there a vicious circle between autoimmune diseases and SARS-CoV-2 infection? The outcome of SARS-CoV-2 re-infection in autoimmune diseases is unclear. To date, there are no established specific therapies for this novel disease. We hope this work may contribute in a significant way to the understanding of the association between patient with AIDs and COVID-19 infection.

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**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

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