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Immunopathogenic and therapeutic profile of Covid-19: A comprehensive approach to explore Covid-19

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Abstract
COVID-19 is a disease caused by the novel strain of coronavirus also known as SARS-CoV-2 initially originated in Wuhan, China. On March 11, 2019 it was officially declared as a global pandemic by WHO. The viral transmission was associated with respiratory droplets and through other bodily secretions as well. The cellular entry of virus was associated with angiotensin converting enzymes 2 receptors (ACE-2 receptors). This study was conducted from December, 2020 to March, 2021. A total of 159 studies related to immune pathogenesis and therapeutic profile of COVID-19 were included. All studies involving pharmacological therapies for treating COVID-19 were included but the studies manifesting nutritional interventions and herbal medications for treatment of COVID-19 were excluded. Various data bases like Medline/PubMed, Scopus, and web of science were used as a search engine. Fever, cough, myalgia, headache and shortness of breath were common symptoms associated with COVID-19. The clinical spectrum of disease was ranging from asymptomatic carriers to acute respiratory distress syndrome (ARDS) caused by exaggerated inflammatory response also known as cytokine storm (IL-6, IL-1, IL-8, IL-10), and hyperactivity of host immune system (innate, cellular and humoral immune system) leading to severe form of COVID-19. Various therapeutic options used to treat COVID-19 are corticosteroids, antimalarials (hydroxychloroquine and chloroquine), antivirals (Remdesivir, lopinavir/ritonavir), antibiotics (azithromycin), interleukin-6 inhibitors (tocilizumab), Plasma exchange, and finally the most effective and economical treatment is through vaccine which is now considered definitive treatment option. However, more studies are required to explore the most effective, safer and accessible treatment options to treat and prevent COVID-19.

Keywords: Covid-19, cytokine storm, immunopathogenic profile, therapeutic profile

Introduction

Viral Characteristics and Taxonomy

Viruses are classified as obligate intracellular particles that require a living body for their replication and reproduction by using host machinery as the replication factory [1]. The viral capsid is considered an important component of viral morphology, responsible for maintaining the shape and structure of the viral cell as well as protecting its nucleic acid [2]. Viral infections are considered a real threat to the whole world according to the World Health Organization (WHO), one that affects human indiscriminately. Viruses have been responsible for worst outbreaks and global pandemics in recent history, such as the 2009 swine flu pandemic which was caused by H1N1 virus, the various outbreaks of Middle East respiratory syndrome, caused by the MERS-CoV, in the past two decades [3].

The novel strain of coronavirus, also known SARS-CoV-2, is the cause for coronavirus disease 2019. This virus is a member of the same family to which both MERS-CoV and SARS-CoV-1 belong, known as the Coronaviridae family [4]. Coronavirus is a positive-sense, single-strand, non-segmented, enveloped RNA virus that contains nucleocapsid comprising both nucleic acid and capsid proteins, as observed under the electron microscope [5]. According to genomic characterization, the coronavirus is classified into various genera, namely, α-CoV, β-CoV, γ-CoV, and δ-CoV; COVID-19 belongs to β-CoV type [6]. The crown-like appearance of the novel coronavirus (nCoV) was attributed to the presence of spike proteins, also known as S-Proteins, along with membranous proteins (M-proteins) and envelope proteins (E-proteins) on the viral surfaces, with specific role of S-proteins in determining the host tropism and transmission [7]

Viral Transmission and Entry

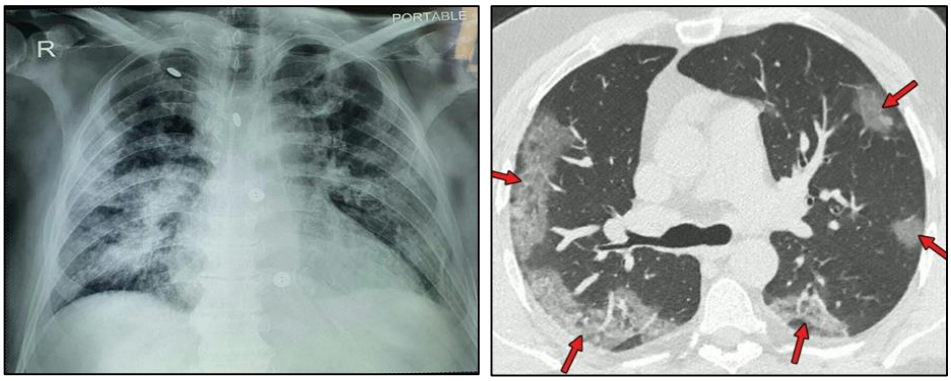
On March 11, 2020, the World Health Organization officially declared that world is going to face another pandemic. The city of Wuhan, China, was the mainland where the first case of COVID-19 was detected [8, 9]. Human-to-human transmission was identified as the source of the spread of the virus, with spread occurring from one person to another through direct contact or through bodily secretions like respiratory droplets [10]. After carefully assessing the morphology of the coronavirus using electron microscopes, the virus was observed to have spike proteins, also called S-proteins, on its surface (Figure 1), two domains of S-proteins, S1 and S2, with a significance of binding capacity with angiotensin-converting enzyme 2 (ACE2) receptors through the receptor-binding domain (RBD) present on the C-terminal point of domain S1; however, S1 domain is considered more immunogenic. A new mechanism of viral entry is delineated through proteolytic cleavage of S2 portion leading to viral fusion with cell membranes and entry into the cells [11]. This mechanism of binding with ACE2 receptors was considered the entry point of the virus into the cells, as these receptors are highly expressed on airway epithelial cells, leading to viral entry into the lungs and causing pneumonia as milder manifestation, and acute respiratory distress syndrome and multi-organ failure (MOF), representing the severe manifestation of the COVID-19 [9].

Clinical Manifestations of COVID-19

The incubation period is normally 3–5 days (within 14 days); however, the mean incubation period was identified as 5.2 days [12]. The most common symptoms associated with novel coronavirus, as found in 99 cases of COVID-19 in Wuhan, China, were fever (83%), dry cough (82%) and shortness of breath (31%); however, some less-common symptoms also manifested like myalgia (11%), headache (8%) and gastrointestinal disturbances (3%) [13, 14]. The severity of the disease ranges from mild to extremely severe, even leading to acute respiratory distress syndrome (ARDS) and ultimately respiratory failure [15, 16]. The most common risk factors identified for the severity of COVID-19 were pre-existing comorbidities related to cardiovascular systems, respiratory systems, hypertension, diabetes and cerebrovascular abnormalities [17, 18]. However, most patients remain asymptomatic carriers; only some present with typical features of pneumonia and 10%–13% of the patients present with strong indications for mechanical ventilation and ICU admissions [19].

Radiological findings and COVID-19

The radiographic findings were also consistent with findings of severe pneumonia, showing patchy consolidations on X-ray caused by infiltration of inflammatory cells leading to bilateral focal ground glass opacities (GGO) more commonly in lower and middle lobe of lungs. However, in the CT-scan findings of the severe form of COVID-19 was found to be associated with massive, multifocal, bilateral ground glass opacities (GGO) with peripheral distribution along with air bronchogram sign [20].



A B

Fig 1: (A) Representing the chest X-ray (Antero-Posterior view) of a severely affected 52-years old male COVID-19 patient, showing the patchy consolidations and fibrosis in both lungs predominantly in lower zones. **(B)** A 47-year-old man with positive RT-PCR test results for SARS-CoV-2, showing bilateral areas of ground-glass opacities (Red arrows) in a peripheral distribution [20].

Laboratory findings and COVID-19

Covid-19 infection is associated with significant immune mediated inflammatory process through release of various pro-inflammatory cytokines known as cytokines storm. Various published literature is showing the significance of these inflammatory mediators in the disease severity and poor prognosis, affecting directly on lungs and various body organs leading to multi-organ failure (MOF) [21], [22]. SARS-CoV-2 is associated with activation of innate and adaptive immunity leading to abnormal immune responses causing tissue damage, either locally or systemically. The severe form of Covid-19 is associated with lymphopenia (<1.0 × 109/L), with reduced levels of CD4+, CD8+ lymphocytes, B-cells and natural killer (NK) cells, eosinophils, basophils and monocytes were also found to be reduced in numbers [23, 24]. However, some studies are also manifesting the role of various inflammatory and pro-inflammatory cytokines like interleukin-6 (IL-6), IL-1β, IL-2, IL-8 and tumor necrosis factor (TNF) were found to be elevated along with C-reactive proteins (CRP) and D-dimer, collectively known as cytokines storm [25]. However, aforementioned changes were not significantly associated with milder forms of Covid-19. The involvement of inflammatory process and immune system dysregulation opens the gates for various anti-inflammatory medications and use of glucocorticoids for treatment of mild to severe forms of Covid-19. The motive of this systematic review is to explore the possible immuno-inflammatory process involved in pathogenesis of COVID-19, and various treatment options we have to cope with this deadly coronavirus.

Methods and Materials

This qualitative systematic review was undertaken from December 2020, to March, 2021 for exploring immuno-

inflammatory processes involved in pathogenesis of COVID-19, and to find various therapeutic options for dealing with novel coronavirus.

Eligibility criteria

We included all those studies (cross-sectional, reviews and clinical trials) that were manifesting the pathogenesis of COVID-19, including those studies that were showing various immunological and inflammatory processing leading to COVID-19, irrespective of severity of the disease. Studies involving various pharmacological therapies for treating COVID-19, were also included in our study. All those studies involving the nutritional interventions, and herbal medications were excluded from our study criteria.

Information sources

An English-language literature search was done through Various search engines like PubMed, Medline, web of science, EBSCO, EMBASE, Google Scholar, and WHO Covid-19 website. Search terms included COVID-19 and Immunopathology, COVID-19 and Cytokine storm, COVID-19 and therapeutic agents. A total of 7820 articles were found after initial searching; however, after searching specific keywords we found 190 articles of our interest and out of them 4560 were excluded because of duplication and finally 159 articles were deemed suitable to involve in our study. Throughout, studies selections (PRISMA) guidelines were followed.

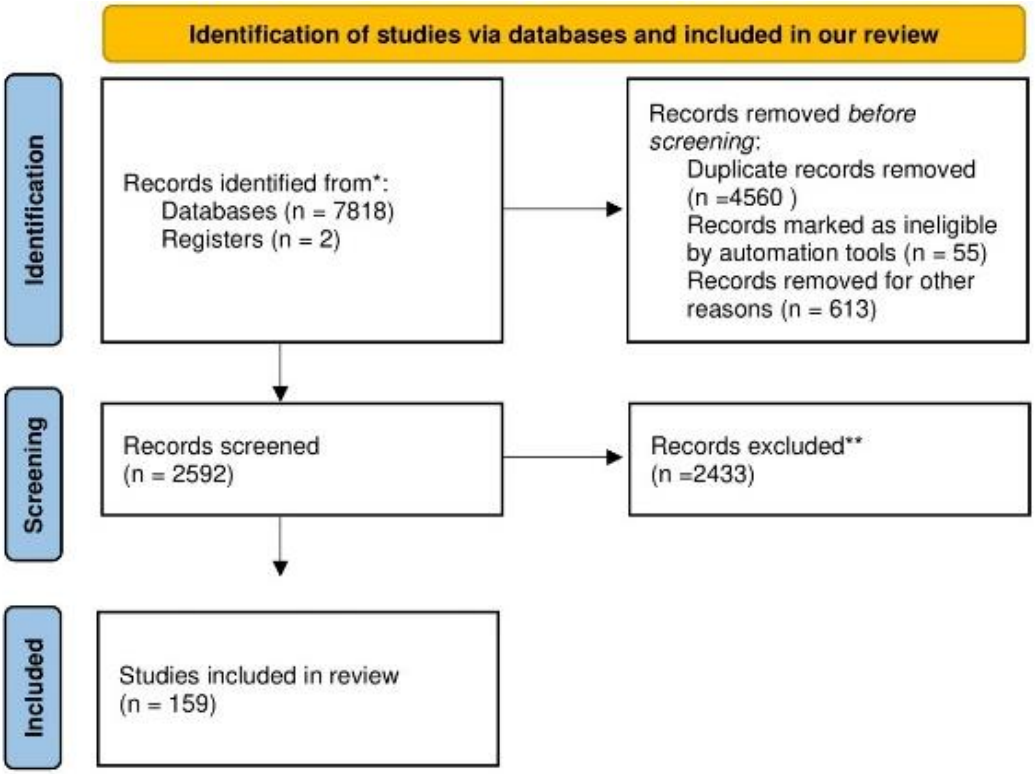


Fig 2: Prisma flow chart for selection of studies

COVID-19 and Immune-inflammatory process:

The novel coronavirus (nCoV) is posing continuous challenges to the health care system's around the globe and scenario is still getting worse day by day. COVID-19 infection is significantly associated with hyperactivity of host immune system, with aggressive production of pro-inflammatory cytokines, known as "cytokines storm". Cytokines are considered part and parcel of an inflammatory process produced exclusively by various T & B lymphocytes, macrophages, dendritic cells and natural killer (NK) cells [22]. As far as coronavirus morphology is concerned, it is consisted of capsid proteins, nucleic acid and various spikes proteins called as crown-like spikes present on the surface of SARS-CoV-2 [26]. The spike S-proteins are consisted of various receptor binding domain (RBD) having strong affiliations for angiotensin-converting enzyme 2 (ACE2) receptors expressed abundantly on the airway epithelium, causing increased uptake of virus into the cells through endocytosis [27, 28].

Innate immune response and COVID-19

Another proposed mechanism of viral entry is through infection of haematopoietic cells and various peripheral blood mononuclear cells (T lymphocytes, B lymphocytes, Natural killer (NK) cells and monocytes), as these cells are associated with abortive replication of virus leading to aberrant production of various chemokines and cytokines [29]. As soon as, virus gets entry into the body its natural response of body to fight against that particular foreign particle, and this function of self defence is accomplished by activation of body innate as well as acquired immune systems. The activation of innate immunity is associated significantly with production of cytokines such as IL-6, IL-1 and TNF-α from macrophages, endothelial and mast cells leading to increased disease severity among patients suffering from COVID-19 [30]. After analysis of cytokines in 41 COVID-19 confirmed cases in China, the levels of IL-8, IL-1β, IL-7, IL-9, lL-10 and TNF-α levels were found to be exceptionally high as compared to healthy controls, similarly in the same study was

also showing increased levels of G-CSF, GM-CSF, MCP-1, MIP-1A along with INF-gamma and VEGF in both patients admitted in ICU and non-ICU [31].

With the passage of time the pathophysiology of COVID-19 has become very clear and explanatory. Various literature is showing different types of immune and cytokines mediated inflammatory processes leading to COVID-19. The explicit role of innate immunity is considered an initial event of this immune-inflammatory process with increased production of acute phase reactants such as C-reactive proteins (CRP), ferritin, erythrocyte sedimentation rate (ESR) and amyloid A [32, 33]. Many studies are manifesting the predictive severity of COVID-19 among those who are having increased levels of cytokines and chemokines. A multicenter retrospective study conducted in Chine, involving 150 confirmed cases of COVID-19 patients was showing the involvement of increased levels of IL-6 among those died of diseased severity (n=68); however, on the flip side IL-6 levels were either low or undetectable among 82 survivors [34]. A similar, study undertaken in China was also showing the involvement of IL-6, IL-10 and TNF-α in severely affected cases of COVID-19 as compared to moderately affected confirmed cases of COVID-19 [35].

On the basis of bronchoalveolar fluid (BALF) analysis, the levels of inflammatory infiltrates were found to be high in the lung tissues of patients suffering from severe form of COVID-19 [36]. The role of macrophages and monocytes was found to be of paramount significance when expression of ACE2 receptors, the binding and entry site of (SARS-CoV-2), were observed on the surface of alveolar macrophages on the bronchoalveolar fluid (BALF) analysis [37]. The severity of COVID-19 was attributed to failure of shifting process of pro-inflammatory (M1) phenotype of macrophages to wound healing (M2) phenotype with enhanced inflammatory response and fibrosis associated with acute respiratory distress syndrome (ARDS). The same inflammatory trend was also observed in (SARS-CoV-1), as is consistent with (SARS-CoV-2) infection [38]. Soon after invasion of Coronavirus (nCoV) into the body innate immune system respond by conversion of circulating monocytes into macrophages and dendritic cells that ultimately leads to increased inflammatory response in the lungs and other body parts [39]. A recent study is also depicting the role of monocytes through production of CD14+ and CD16+ cells leading to increased responsive of GM-CSF+ and increased secretion of IL-6 causing extensive tissue damage validating the role of innate immunity against Coronavirus (nCoV) [37].

Cellular immune response and COVID-19

Evidence based dynamic alteration of acquired immunity between mild and severe forms of COVID-19 was observed after carefully analyzed data of lymphocytes and subset counts through a longitudinal study. The early phase of COVID-19 was found to be associated with decreased numbers of lymphocytes with dramatic loss of natural killer cells (NK) along with CD4+, CD8+ and CD3+ T cells in patients suffering from severe form of COVID-19 [40]. On the flip side, the lymphocytes were found to be raised during early period among patients suffering form milder form of COVID-19 infection; however, during the late course of the disease the level of lymphocytes in severely affected COVID-19 patients reached to the levels observed in milder form of the disease [39]. Additionally, the Th1 and Th2 related cytokines particularly INF-gamma, IL-5, IL-4 and IL-13 becomes activated and detectable as after the invasion of virus in the body. leading to recruitment of inflammatory cells like neutrophils and eosinophils along with differentiation of B-cells leading to antibody productions validating the role of adaptive immunity against (nCoV) [30].

A study also observed the role of S-RBD-specific T cells and NP-specific T cells, that were found to be high in patients suffering mild to moderately severe COVID-19. A mild correlation was also observed between viral-specific T cells and neutralising titers corresponding the value of adoptive immunity [41]. In a closely monitored mild COVID-19 case the levels of antibodies producing B-cells and T cells (CD4+, CD8+ cells) were found be high just before symptoms start resolving and their levels were observed to be at a steady state through out the convalescent phase. At that point diseases course viral replication became undetectable and robust viral clearance was also observed [42]. Flow cytometric analysis report of severe COVID-19 patients was also depicting the high levels of CD4+ T cells derived Th17 in the blood; however, the levels of cytotoxic CD8+ T cells were found to be high in lung tissues. Excessive cytotoxic CD8+ amount in lung tissues along with Th-17 induced inflammatory responses were speculated to be partly responsible for lungs injury due COVID-19 [36]. Excessive Th-17 production along with its associated cytokines storm was playing a paramount role in inflammatory injury of lungs. Based on this observation, the role of specific inhibitors targeting Th-17 induced inflammatory pathways is considered a therapeutic miracle through inhibition of JAK-2 signalling pathways that help in Th-17 cells differentiation. The JAK-2 inhibitor like (Fedratinib) is considered an effective drug option in Th-17 dominant immune profile [43].

Cytokines production and COVID-19

Soon after viral invasion into the body, a rapid and coordinated immune response become activated leading to production of various cytokines acting as a defence mechanism against viral attack [29]. Previous literatures related to SARS-CoV-1 and MERS-CoV is found to be signifying the role of dysregulated cytokines production through innate and adaptive immune system. An experience form past SARS-CoV infection it was found that various immune cells and infected hematopoietic cells including monocyte-macrophages were found enhanced proinflamatory cytokines (IL-6, INF-α or INF-gamma, TNF-α) production [44]. In the same vein, MERS-CoV infection causes delayed but robust production of various pro-inflammatory cytokines like IL-1β, IL-8, IL-6, along with increased production of INF-α [45, 46]. In studies published in pandemic outbreak, the cytokines and chemokines involved in pathogenesis of COVID-19 were carefully analysed and their impact on disease outcomes were elucidated [35, 45, 46]. Significant production of various cytokines like, IL-1β, IL-1ra, INF-gamma, IP-10, and MCP-1, MCP-3 were observed in critically ill patients [40]. The alteration in various cytokines production pattern, and levels of lymphocytes and T cell related CD molecules were negatively correlated, validating the association between cytokine storm and adaptive immunity. During acute phase of the disease, the elevated levels of lymphocytes were not accompanied by robust increase in various cytokines levels, and this concept was attributed to the role of cellular immunity with rapid viral clearance [39].

Various studies are showing a unique role of plasmacytoid

dendritic cells (pDCs) in pathogenesis of COVID-19 through production of INF-I [47]. The increased levels of INF-I were found positively correlated with disease severity; however, this is in contrary to what is observed in SARS infection, where reduced levels of INF-I were associated with reduction in disease severity [47]. This INF-I induced immune dysregulation is considered the triggering factor in aggravation of COVID-19 severity. The dysregulated immune response of body is found to be associated with hyperactivation of cytokines and resulting disease deterioration. The robust increase in cytokines production, also known as cytokines storm exerts pathogenic rather than protective impact on host [40]. Studies are also showing the elevated levels of various chemokines receptors (CC) like CCR4+ and CCR6+ Th-17 cells in COVID-19 [36].

Humoral immune response and COVID-19

Many scholars have done wonderful work for explaining the dynamics of antibodies against novel coronavirus (nCoV), as antibodies are considered a potent diagnostic tool to complement RT-PCR based positive COVID-19 cases [48]. Studies are showing the role of humoral immune system's in terms of antibodies production against SARS-CoV. Immunological (humoral) response against SARS-CoV is manifested through production of viral specific IgM specific primary response that reached at peak within 4 weeks to undetectable levels of IgM at 3 months post symptoms onset (PSO) with switching to IgG around day 14; however, the levels of IgG remain raised up to 36 months [49, 50]. A study conducted to analysed the dynamics of antibodies response in 34 SARS-CoV-2 positive confirmed cases, showed the increased levels of IgM and IgG at 3 weeks post symptoms onset (PSO), IgM levels were found to be decreased around 4th week while 2 patients were negative at around 5th week and additional 2 patients became negative around 7th week. On the flip side levels of IgG raised gradually form 3rd week to 7th week validating the role of humoral immunity against SARS-CoV-2 [51]. Kai-Wang To et al. showed the elevation of antibodies titers around 1st week post symptoms onset (PSO) and majority of the patients showed seroconversion within 3 weeks, speculating that the humoral response of SARS-CoV-2 is similar to that of manifested by SARS-CoV [52].

As soon as virus gets entry into the target cell, host immune system gets activated and recognised viral whole surfaces and its associated epitopes leading to innate and adaptive immune response. The presence of Pathogen recognition receptors (PRRs) like Toll-like receptor 3, 5, and 8, present on immune cells, are considered first to interact with virus and leads to robust production of interferon (INF) [53]. The humoral response against SARS-CoV-2 is also found to be similar, as in others coronavirus infections, involving significant production of IgM as a primary response and IgG through secondary response. Soon after viral entry host B-cells start producing antibodies against N-protein, though similar response against S-protein is also detected with in 1-2 weeks after appearance of initial symptoms [54]. Morphological assessment of SARS-CoV-2 also shows that N-proteins are smaller than S-proteins, but N-proteins are considered highly immunogenic with absence of glycosylated sites on them leading to production of neutralizing antibodies [55]. An observational study conducted in 16 COVID-19 patients delineated the production of anti-S-RBD IgG in all of the subjects; in the same vein, anti-N-RBD IgG and anti-S-RBD IgM was found in 15 subjects and 14 patients were also showing anti-N-RBD IgM production in the disease course [52]. An ELISA-based kinetic study also delineated the role of IgM and IgG production with COVID-19 severity, showing that increased production of both IgG and IgM were found to be associated with more severe disease, while weak responders of antibodies production were showing viral clearance at higher rates as compared to strong responders [56].

Guo et al. delineated the role of early antibodies production against NP-proteins of SARS-CoV-2 infected patients, showing that 90.4% and the 93.3% of 208 SARS-CoV-2 infected patients were tested positive for IgM and IgA; however, 77.9% of patients were harbouring IgG as well. The mean duration of IgM and IgA production was at day 5 (IQR-3-6), in the same vein the mean duration of IgG production was found to be 14 days (IQR-10-18) post symptoms onset (PSO) [57]. Additional reports on the dynamics of antibodies in patients infected with SARS-CoV-2, showed sequential seroconversion of total antibodies, IgM and IgG, with a median time of 11, 12, and 14 days [48]. A study conducted on paediatric patients also showed the protective role of humoral immune response, showing that neutralizing antibodies IgM and IgG targeted against N and S-RBD of SARS-CoV-2 were found in 5 out of 6 infected patients validating the protective role of neutralizing antibodies in children [58]. On the flip side, the role of non-neutralizing antibodies has also been demonstrated that leads to ACE-2 independent pathways of viral entry into the cells (immune & antigen presenting cells APCs) with no viral replication; however, viral shedding and by macrophages enhance immune mediated inflammatory process leading to tissue injury through myeloid cells activation. This non-neutralizing antibodies mediated viral entry and aberrant immune cells activation is called antibody dependent enhancement (ADE) [59, 60].

The role of antibody dependent enhancement (ADE) has already been extensively investigated in other viral infections like Ebola, HIV and dengue, and ADE role was most commonly attributed to severity of disease [61, 62, 63]. Tetro et al. Speculated the priming effects of coronavirus, showing that those who were already infected with one or more coronavirus were manifesting the severe form of SARS-CoV-2 infection, leading to antibody dependent enhancement (ADE) [64]. A proposed mechanism of severity of reinfection from SARS-CoV-2 was also delineated by various studies, showing that antibodies elicited from previous infections were not able to completely neutralize the second infection, leading to complimentary viral complex formation that was found to interact with Fc or complement receptors permitting viral entry into the susceptible cells [65]. On the flip side, some studies are not validating this concept of cross-reactivity and ADE [66]. Similarly, Amanat and collaborators also nullifying the concept of ADE, and its association with disease outcomes and pathogenicity [67]. New investigations are needed to explore the antibody dependent enhancement (ADE) mechanism in order to get putative effects of antibody-based therapies and to address viral specific vaccine design.

Therapeutic profile of COVID-19

Corticosteroids and COVID-19

Anti-inflammatory and anti-fibrotic properties of corticosteroids have been utilised in suppressing lung inflammation and fibrosis caused by COVID-19 [68]. The role

of corticosteroids in treating COVID-19 patients have been best depicted by its mechanism of improving dysregulated immune response caused by viral attack [69]. Low doses of corticosteroids cause down regulation of proinflamatory cytokine transcription, resulting in reduced cytokines response and accelerating the resolution of inflammatory response in the lungs, reducing duration and severity of pneumonia [70]. The most commonly used corticosteroids for COVID-19 were dexamethasone and methylprednisolone. Preliminary reports from RECOVERY trail were showing the effectiveness of dexamethasone against severe form of COVID-19 and low-dose dexamethasone 6mg once daily either orally or intravenous for 10 days, was found to be most effective dose against COVID-19 leading to reduction in overall mortality among one third of patients on mechanical ventilation [71]. Similarly, another multicentre randomized controlled trial (DEXA-COVID19), involving the mechanically ventilated patient's of COVID-19 also demonstrating the effectiveness of dexamethasone (20mg once daily I.V for day 1-5, followed by 10mg daily from day 6-10) in terms of reducing the duration of mechanical ventilation dependence (NCT04325061) [72].

Several Retrospective, observational studies have demonstrated the effectiveness of methylprednisolone against COVID-19. A similar, study conducted by Wang et al, have depicted the role of methylprednisolone (1-2mg/day, I.V for 5-7 days) in reducing average number of days for fever resolution and marked improvement of SpO2 in 26 patients out of severely affected 46 confirmed COVID-19 cases [73]. The use of high doses of methylprednisolone has also been demonstrated for treatment of cytokines storm. The effective dose of 60-125 mg every 6 h for 3 days have been shown to reduce the severity of COVID-19 secondary to increased levels of CRP and cytokines; however, tapering of dose is recommended as CRP levels begin to decline [74]. In the same vein, the use of hydrocortisone has also been shown in a retrospective observational study involving critically ill patients suffering MARS infection with a recommended dose of 300 mg per day, but no significant benefit was observed in this study [75]. Though studies are showing the effectiveness of corticosteroids in severe form of COVID-19, but on the other hand data is clearly depicting the harmful side effects that are outweighing the benefits against COVID-19. The most commonly encountered side effects are delayed viral clearance, prolonged viremia, avascular necrosis, hyperglycemia, osteoporosis and water and salts retention (less common in methylprednisolone), limiting their utility and effectiveness against COVID-19 [68, 76].

Chloroquine, Hydroxychloroquine and COVID-19

The immunomodulatory properties of antimalarials such as Hydroxychloroquine and Chloroquine has been well postulated as a therapeutic agent against viral infections [77, 78]. Anti-inflammatory properties of both Hydroxychloroquine and Chloroquine is best delineated through reduction in cytokines (IL-6 & IL-1) production as well as through inhibition of Toll-like receptors signalling [79, 80]. Aside from antimalarials activity, the immunomodulatory properties of both Chloroquine and its derivative Hydroxychloroquine has also been utilized in treatment of various autoimmune diseases like Rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [81]. In the same vein, the role of antimalarials as an anti-inflammatory agent have delineated their effectiveness against COVID-19 as well [82].

Chloroquine and its derivatives are considered weak bases, and in their non-protonated form they penetrate, and concentrate in the intracellular organelles that are acidic in nature, such as lysosomes and endosomes. Soon after entry into the cells Chloroquine and analogs become protonated with resultant increase in cellular pH, resulting dysfunctional enzymes activity and reduced synthesis of proteins [83]. The alteration in cellular pH results in inhibition of viral replication and reduced viral entry into the cells and late transport of enveloped virus. The aforementioned mechanism of Chloroquine and analogs have been implicated in treatment of COVID-19 as well. However, Chloroquine has been shown to inhibit the terminal glycosylation of ACE2 receptor, prevention SARS-CoV-2 recognition, binding and cellular entry [84].

The tablet formulation of Chloroquine phosphate, with prescribed dosage of 500 mg orally taken twice daily for two weeks, has been implicated in the treatment of COVID-19 [85]. However, the estimated bioavailability is found to be almost 60-100% with in half an hour. The Chloroquine is found to be distributed to almost every organ of body including eyes, kidney, lungs, and liver [86]. Similarly, Hydroxychloroquine is used as film-coated tablet formulations for oral administration. However, the dosage adjustment against COVID-19 is not well understood, but a dose of 400 mg orally twice daily on day 1 followed by a dose of 200mg twice daily for next 4 days duration is recommended [87]. The safety profile of Chloroquine is found to be better as compared to Hydroxychloroquine, having 3-folds higher cytotoxic potential but the fact behind higher cytotoxic potential is still least understood mechanism [88]. The most common adverse effects associated with the use of both Chloroquine and Hydroxychloroquine are gastrointestinal intolerances like nausea, vomiting, abdominal cramps and taste disturbances. However, QTc prolongation is also a serous adverse event associated with the use of antimalarials [89]. The impending risks of acute toxicity of Chloroquine and Hydroxychloroquine (neuropathy, retinopathy, cardiomyopathy & myopathy) has limited the utility of antimalarials against COVID-19, however, it's still considered as a treatment choice in many settings.

Anakinra and COVID-19

Anakinra is an IL-1 receptor antagonist having wide variety of therapeutic indications like rheumatoid arthritis, cryopyrin-associated periodic syndromes, still's disease and familial Mediterranean fever when used with dose of 100 mg subcutaneously [90]. The use of anakinra against COVID-19 is well validated through its effect of inhabiting pro-inflammatory cytokines (IL-1α and IL-1β) and combating cytokine storm [91]. Hyper-inflammatory response in COVID-19 patients is associated with significant cytokines production like IL-1, IL-6, IL-8 and interferon-γ [92]. Anakinra is found to be effective drug in combating hyper-inflammatory response associated with COVID-19 [93]. According to a phase III randomized controlled trail, the high dose of anakinra with its IL-1RA effect is found to improve the survival rate among patient's with sepsis [94]. A total dose of 400 mg daily in divided dosage 100 mg for every 6 h either intravenously (IV) or subcutaneously (SC) is recommended to used against COVID-19; however, the intravenous route is still not approved by FDA [95]. Many randomised controlled

trial (NCT04356366, NCT04339712, NCT04330638) are underway to approve the efficacy of this drug against anakinra and to make it available as a standard treatment option. The side effects associated with the use of anakinra are headache, nausea, vomiting, abdominal pain, diarrhoea and flu-like illness, but these side effects are of least significance when compared with its effectiveness against COVID-19 [96].

Azithromycin and COVID-19

Azithromycin is one of the macrolides having both anti-inflammatory and immunomodulatory effect, and proposed as treatment option for respiratory infections including COVID-19 [97]. The immunomodulatory effects of azithromycin have been manifested in two different phases of the disease: during the acute phase and during recovery phase of the disease. In the acute phase of the disease it cause reduction in production of pro-inflammatory cytokines like TNF-α, MMPs, interleukin-8 (IL-8) and IL-6; however, during resolution phase it causes neutrophilic apoptosis and oxidative stress related with inflammation [98]. In the same vein, another proposed mechanism of azithromycin is reduction in acidic environment in endosomes through its properties of being a weak base. The acidic environment in endosomes is required for viral replication, but azithromycin because of its basic nature inhibits viral replication [99]. A recent mechanical quantum modeling have shown the role of azithromycin in preventing the SARS-CoV-2 binding through its spike proteins with host ACE2 receptors, but more studies are required to validate this effect of azithromycin [100].

Many studies have investigated the in vitro antiviral activity of azithromycin against viral pathogens with 50% inhibitory concentration (EC50) of ~1-6 µM. In the same vein, the EC50 for SARS-CoV-2 is found to be 2.12 µM [101]. The recommend dose of azithromycin is 500 mg on day one followed by 250 mg for 2-5 days [102]. There are number of studies showing the effectiveness of combined azithromycin and Hydroxychloroquine against COVID-19. A study by (Gautret et al) showed the favourable outcomes in 81.3% of the patients in terms of mortality and period of hospital stay by using the combination of both azithromycin and hydroxychloroquine leading to reduction in viral load by 83% on day 6 of the treatment [102, 103]. However, in a retrospective multicenter cohort study conducted on 1438 hospitalized patients of COVID-19, out of 1438 confirmed cases of COVID-19 only 735 patients were administered both azithromycin and hydroxychloroquine and other patients were given either hydroxychloroquine alone, azithromycin alone and some were not receiving any of the above-mentioned treatment. On comparing the hospital mortality rate among these four groups no significant difference was observed in any of the above groups [104]. The associated side effects of using this combination was prolongation of QTc interval greater than 500 msec and some patients also reported to have cardiac arrest as well, limiting the utilization of this combination regiem in patients of COVID-19 [105].

Tocilizumab and COVID-19

Tocilizumab (Actemra®) is a recombinant humanized monoclonal antibody that help in preventing binding of IL-6 with IL-6 receptors, and because of its anti-inflammatory action it has already been used for treating rheumatoid arthritis (RA) [106]. Tocilizumab is also known to be a biological disease modifying anti-rheumatic drug (BoDMARD) being used as an alternative to tumor necrosis factor (TNF-α) antagonist and methotrexate, having excellent safety profile [107]. As far as COVID-19 perspective elevated levels of IL-6 are associated with poor prognosis [108]. Tocilizumab helps in downregulating the IL-6 associated inflammatory response by binding to membrane bound IL-6 receptors (mIL-6R) and soluble IL-6 receptors [109]. A study from Wuhan, involving 20 patients of COVID-19, was showing excellent response in terms of reduction in fever spike, improvement in oxygenation and discharge from hospital in 95% of the patients who were given tocilizumab [110]. Similarly, another retrospective, observational study involving fifteen moderate to critically ill patients of COVID-19 were also showing significant reduction in acute phase CRP following administration of tocilizumab and gradual reduction in IL-6 as well [111]. The recommended dose of tocilizumab is 400 mg (4-8mg/kg), with one extra dose after 12 h and a maximum dose of 800 mg intravenously (IV) [112]. The average half-life of tocilizumab is concentration dependent that is about 11 days when used in concentration of 4 mg/kg and 13 days with concentration of 8 mg/kg [113]. The side effects profile associated with tocilizumab are mostly infusion reactions such as headache, hypertension, skin reactivity and sometimes making the patients prone to infections either bacterial, viral and fungal [114].

Remdesivir and COVID-19

Remdesivir is a 1-cyano-substitued adenosine nucleotide analog [115]. The use of remdesivir was initially approved for treatment of Ebola haemorrhagic fever, however to validate its effectiveness even against Ebola virus is still under consideration of many trials but no effective results have been postulated up-to the date [116]. To validate effectiveness of remdesivir against COVID-19, this drug is still in an investigational phase undergoing phase III clinical trial but some studies have reported the effectiveness of this drug against MERS-CoV, SARS-CoV, and SARS-CoV-2 [117]. After entering in cell and tissue remdesivir is converted into an activated nucleoside triphosphate and inhibit RNA-dependent RNA polymerase, thus inhabiting viral replication [117]. Another proposed mechanism of remdesivir is through its exo-ribonuclease action and viral clearance [118]. According to undergoing clinical trials a loading dose of 200 mg intravenously followed by 100 mg IV for 5-10 days has been a recommended dose to be used in humans (NCT04252664, NCT04257656) [119, 120]. Some studies are depicting the effectiveness of remdesivir against coronavirus when studied in the lung model and when airway epithelial cells were analysed, but data is insufficient to validate its effectiveness against COVID-19 as a standard treatment option [121]. The side effects profile associated with remdesivir was nausea, vomiting, gastroparesis, rectal bleeding and derangement in liver enzymes profile particularly aminotransferases; however, its not very clear that elevated liver enzymes were either due to drug usage or due to COVID-19 itself as this infection itself causes derangement in liver enzymes profile [122].

Lopinavir/Ritonavir (LPV/r) and COVID-19

Lopinavir is an aspartic acid protease inhibitor initially developed and used for treatment of HIV, and considered a standard therapeutic option along with other anti-retroviral therapies for treatment of AIDS patients [123]. Lopinavir is

used in co-formulation with ritonavir with special effect of increased half-life and drug effectiveness by decreasing metabolism through inhibition of CYP450 [124]. Through its structural similarity with C2 catalytic site in protease portion of HIV this drug was instituted to work as an anti-protease and inhibit viral replication in patients with HIV [125]. However, on the other hand SARS-CoV-2 belongs to a cysteine protease family having no C2 catalytic site and having structural dissimilarities with LPV [126]. The rationale of using LPV/r for treatment of COVID-19 is due its capability of inhibiting 3-chymotripsin like protease found in novel coronavirus [127]. According to a randomized controlled open-label trial 199 confirmed SARS-CoV-2 positive cases were recruited for randomization. Out of total 199 patients 99 were assigned be the lopinavir-ritonavir group and remaining 100 patients were assigned as standard care group. A dose of 400 mg twice daily for lopinavir and 100 mg twice daily for ritonavir was administered for 14 days, however, no significant difference in mortality and clinical improvement was observed in those undergoing treatment with lopinavir-ritonavir as compared to standard care group [128]. Similarly, up-to the date studies are not providing sufficient evidences in the favour of using this treatment in COVID-19 patients. The side effects associated with the use of LPV/r are diarrhoea, pancreatitis, hepatitis, and prolongation of PR interval particularly in those having congenitally prolonged QTc syndrome [129].

Similarly, Favipiravir a nucleoside analogue is also known to have anti-viral activity against influenza A and B. However, its effectiveness against COVID-19 is still under clinical trial phase with some success in terms of reducing duration of fever and cough has been demonstrated by clinical trials conducted in China and Japan [130]. In the same vein, oseltamivir is another antiviral agent used to treat viral infections through its neuraminidase inhibitory potential but its also in trial phase with least understood about its effectiveness against COVID-19 [131].

Baricitinib and COVID-19

Baricitinib (Olumiant®) is a Janus Kinase inhibitor that reversibly and selectively inhibit JAK1, JAK2 and to some extent JAK3 and tyrosine kinase. The dual role of baricitinib is well validated in terms of preventing viral entry and acting as an anti-inflammatory agent in patients with COVID-19 [132]. The effectiveness and safety profile of this drug is very much validated to be used in patients with COVID-19 as compared to other JAK inhibitors (Ruxolitinib) [133]. Another proposed mechanism of baricitinib is prevention of viral (SARS-CoV-2) endocytosis and inhibition of associated protein kinase-1 (AAK1) [7]. The proposed dose of baricitinib is 2 mg/day orally is indicated for treatment of rheumatoid arthritis; however, the recommended dose for treatment of COVID-19 is either 2 mg/day or 4mg/day orally for 14 days [134]. Despite effectiveness of baricitinib in COVID-19 treatment, its use is limited in clinical settings because of adverse effects profile of increasing chances of infections (reactivation of herpes zoster virus), increased chances of malignancy and increased risk of thromboembolism, limiting utilisation of JAK-inhibitors in patient's of COVID-19 [135].

Interferons and COVID-19

Interferons (IFNs) are cytokines that help in reducing viral replication and modulating host immune system in combating against viral infection. IFNs are released by plasmacytoid dendritic cells with production of α and β subtypes [136]. The upregulation of IFNs after viral infection stimulate body immune system and eradicating viral replication and preventing viral spread [137]. This mechanism of viral replication inhibition is also been utilized in treatment of hepatitis B and C through IFN-α [138]. The dosage recommendations of INFs in patient's with COVID-19 has not been established yet because this therapy is still being used as a part of clinical trial; however, a dose of 0.25 mg (8 million IU) has been used for treatment of COVID-19 with interferon-β-1b [139]. The utilization of interferon against COVID-19 require more studies to validate the effectiveness of this therapy. The side effects profile associated with IFNs are fever, malaise, headache, lymphopenia and thyroiditis as well [139].

Anticoagulation and COVID-19

Many studies have reported the association of COVID-19 in causing venous Thromboembolism due to prolonged immobilization, exaggerated inflammatory response and diffuse intravascular coagulation (DIC) [140, 141]. Increased incidence of Disseminated intravascular coagulation is associated with increased in number of deaths in patients with COVID-19 [142]. This observation led to the utilization of anticoagulants like heparin to combat this grave complication of COVID-19 [143]. A study conducted on 27 diagnosed patients of COVID-19 in Brazil who were administered heparin at therapeutic dose were showing marked improvement in arterial oxygen saturation and increased discharge rate of 81% within 12 days [144]. The low molecular weight Heparin (LMWH) acts through inhibition of activated factor X and by inhibiting thrombin. It also reduced IL-6 mediated inflammatory process with improved outcome in patients with COVID-19 [145]. The recommended dosage of LMWH is adjusted according to body weight of the patients, with dose of 4000 IU in patients with <50kg and 6000 IU in patient with 50-70kg weight; 4000 IU twice a day for patients with body weight of 70-100kg and 6000 IU twice daily for patients with body weight of >100kg [146]. This intervention is proving fruitful in reducing the mortality rate among patients with COVID-19, however, still more studies are required to prove its efficacy.

Convalescent plasma and COVID-19

Many studies have demonstrated the effectiveness of plasma transfusion from the patients who have recently recovered from COVID-19 and having high levels of neutralising antibody titer (NAT) [147, 148]. The provision of short-term passive immunity through performed antibodies from recovered patient's of COVID-19 is providing effective treatment option for preventing infection [149]. This strategy of plasma exchange has also been employed in treatment of Ebola, SARS and MERS [150]. In a retrospective comparative study involving 40 patients of SARS infection also demonstrated the effectiveness of plasma exchange with 74% of the patients being discharged on day 22 as compared to 19% of the patients treated with corticosteroids on day 21 of drug administration [151]. A similar study involving five critically ill patients of COVID-19 who required mechanical ventilation were administered with plasma of recovered patients having high levels of neutralizing antibodies were showing reduced viral load with improved prognosis after administration of plasma [152]. Most common side effects are hypersensitivity reaction and allergy to human plasma.

Vaccines and COVID-19

The development and early distribution of vaccines is considered the most effective way of combating with COVID-19. Asymptomatic carriers are the main source of viral transmission and vaccination is an excellent strategy to contain viral transmission and occurrence of disease [153, 154]. The first vaccine used in clinical trials is mRNA vaccine that is administered through lipid nanoparticles [153]. However, there are various types of vaccines, live attenuated vaccines, inactivated vaccines, and viral vectors. The live attenuated vaccine is an avirulent viral vaccine used to prevent and treat COVID-19. It is considered vaccine of choice for COVID-19 patients because of its long-lasting effectiveness [155]. Similarly, inactivated vaccine is prepared by thermal and chemical intervention of SARS-CoV-2, and it is found to be more effective and safer than live attenuated vaccine (LAV) but it requires multiple doses for achievement of an effective levels of immunity [155]. Other available vaccines are viral vectors either adenovirus type-5 vector (Ad5-nCoV) and chimpanzee adenovirus vector vaccine [156]. Other available vaccine are either next generation vaccines and peptide based vaccines are also being utilized in clinical trials to demonstrate their effectiveness. The nucleic acid-based vaccine such as DNA and mRNA are being studied because of their excellent safety profile. A mRNA-based vaccine by Moderna a U.S based vaccine, is being approved by FDA after having success in clinical trial [157]. Another mRNA-based vaccine by Biotech-pfizer has also been approved for mass vaccination [158]. BNT162b2 is a nucleoside-modified RNA encoding full length spikes of SARS-CoV-2 is found to be 95% effective in preventing COVID-19 [159]. Vaccines are now considered only retort to combat COVID-19 and its global utilization has been started.

Conclusion

Covid-19 caused by novel coronavirus is initially identified in Wuhan, China. It was declared as a global pandemic by WHO on 11th March 2020. The most common presenting clinical features are fever, headache, myalgia, and cough. Respiratory droplets and bodily secretions were main source of viral transmission. The severe form of COVID-19 was associated with production of various cytokines (IL-6, IL-1β, IL-1, IL-10 and TNF-α), called as cytokines storm. Human immune system response was also exaggerated leading to acute respiratory distress syndrome. Hyperactivation of Innate immune response (through production of cytokines), cellular immune response (through decreased amount of CD2+, CD4+, CD8+ lymphocytes and natural killer cells), and finally humoral immune response was associated with severe form of COVID-19. The various therapeutic options are available including corticosteroids, IL-6 receptor inhibitors (tocilizumab), antivirals (Remdesivir, lopinavir/ritonavir), anticoagulants (LMWH), antibiotics (azithromycin) and finally the most effective and safer treatment with vaccines. Various vaccines are now available either live attenuated (LAV), inactivated vaccines, viral vectors and nucleic acid-based vaccines like Moderna and Pfizer (mRNA-based vaccines).

Conflict of interest

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References

1. Jeevanandam J, Pal K, Danquah MK. Virus-like nanoparticles as a novel delivery tool in gene therapy. Biochimie. 2019; 157:38-47. https://doi.org/10.1016/j.biochi.2018.11.001.
2. Aljabali AA, Sainsbury F, Lomonossoff GP, et al. Cowpea mosaic virus unmodified empty viruslike particles loaded with metal and metal oxide. Small (Weinheim an der Bergstrasse, Germany). 2010; 6(7):818-821. https://doi.org/10.1002/smll.200902135.
3. Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus. In StatPearls. StatPearls Publishing, 2020. https://pubmed.ncbi.nlm.nih.gov/32150360/.
4. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2020; 91:264-266. https://doi.org/10.1016/j.ijid.2020.01.009.
5. Woo PC, Huang Y, Lau SK, et al. Coronavirus genomics and bioinformatics analysis. Viruses. 2010; 2(8):1804-1820. https://doi.org/10.3390/v2081803.
6. Su S, Wong G, Shi W, et al. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends in microbiology. 2016; 24(6):490-502. https://doi.org/10.1016/j.tim.2016.03.003.
7. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England). 2020; 395(10224):565-574. https://doi.org/10.1016/S0140-6736(20)30251-8.
8. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine. 2020; 382(8):727-733. https://doi.org/10.1056/NEJMoa2001017.
9. Zhan M, Qin Y, Xue X, et al. Death from Covid-19 of 23 Health Care Workers in China. The New England journal of medicine. 2020; 382(23):2267-2268. https://doi.org/10.1056/NEJMc2005696.
10. Wadia R. Transmission routes of COVID-19 in the dental practice. British dental journal. 2020; 228(8):595. https://doi.org/10.1038/s41415-020-1547-1.
11. Chen HX, Chen ZH, Shen HH. Sheng li xue bao: Acta physiologica Sinica. 2020; 72(5):617-630. https://pubmed.ncbi.nlm.nih.gov/33106832/.
12. She J, Jiang J, Ye L, Hu L, Bai C, Song Y. 2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies. Clinical and translational medicine. 2020; 9(1):19. https://doi.org/10.1186/s40169-020-00271-z.
13. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020; 71(15):769-777. https://doi.org/10.1093/cid/ciaa272.
14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases

of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England). 2020; 395(10223):507-513. https://doi.org/10.1016/S0140-6736(20)30211-7.
15. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. The Lancet. Respiratory medicine. 2020; 8(5):518-526. https://doi.org/10.1016/S2213-2600(20)30121-1.
16. Li X, Ma X. Acute respiratory failure in COVID-19: is it typical ARDS?. Critical care (London, England). 2020; 24(1):198. https://doi.org/10.1186/s13054-020-02911-9.
17. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla AE, et al. Covid-19 and comorbidities: Deleterious impact on infected patients. Journal of infection and public health. 2020; 13(12):1833-1839. https://doi.org/10.1016/j.jiph.2020.07.014.
18. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. International journal of public health. 2020; 65(5):533-546. https://doi.org/10.1007/s00038-020-01390-7.
19. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The Covid-19 Cytokine Storm; What We Know So Far. Frontiers in immunology. 2020; 11:1446. https://doi.org/10.3389/fimmu.2020.01446.
20. Kwee TC, Kwee RM. Chest CT in COVID-19: What the Radiologist Needs to Know. Radiographics: a review publication of the Radiological Society of North America, Inc. 2020; 40(7):1848-1865. https://doi.org/10.1148/rg.2020200159.
21. Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. Journal of medical virology. 2020; 92(9):1449-1459. https://doi.org/10.1002/jmv.25822.
22. Fajgenbaum DC, June CH. Cytokine Storm. The New England journal of medicine. 2020; 383(23):2255-2273. https://doi.org/10.1056/NEJMra2026131.
23. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020; 71(15):762-768. https://doi.org/10.1093/cid/ciaa248.
24. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. (2020). Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cellular & molecular immunology. 2020; 17(5):533-535. https://doi.org/10.1038/s41423-020-0402-2.
25. Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, Shi Y. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. Immunology. 2020; 160(3):261-268. https://doi.org/10.1111/imm.13223.
26. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virology journal. 2019; 16(1):69. https://doi.org/10.1186/s12985-019-1182-0.
27. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science (New York, N.Y.), 2020; 367(6485):1444-1448. https://doi.org/10.1126/science.abb2762.
28. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nature communications. 2020; 11(1):1620. https://doi.org/10.1038/s41467-020-15562-9.
29. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Seminars in immunopathology. 2017; 39(5):529-539. https://doi.org/10.1007/s00281-017-0629-x.
30. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020; 395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5.
31. Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cellular & molecular immunology. 2020; 17(5):541-543. https://doi.org/10.1038/s41423-020-0401-3.
32. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020; 395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3.
33. Li H, Xiang X, Ren H, et al. Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis. The Journal of infection. 2020; 80(6):646-655. https://doi.org/10.1016/j.jinf.2020.03.035.
34. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine. 2020; 46(5):846-848. https://doi.org/10.1007/s00134-020-05991-x.
35. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. The Journal of clinical investigation. 2020; 130(5):2620-2629. https://doi.org/10.1172/JCI137244.
36. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet. Respiratory medicine. 2020; 8(4):420-422. https://doi.org/10.1016/S2213-2600(20)30076-X.
37. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. National Science Review, 2020. nwaa041. https://doi.org/10.1093/nsr/nwaa041.
38. Liu L, Wei Q, Lin Q, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI insight. 2019; 4(4):e123158. https://doi.org/10.1172/jci.insight.123158.
39. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. E Bio Medicine. 2020; 55:102763.

https://doi.org/10.1016/j.ebiom.2020.102763.
40. Zhang YY, Li BR, Ning BT. The Comparative Immunological Characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2 Coronavirus Infections. Frontiers in immunology. 2020; 11:2033. https://doi.org/10.3389/fimmu.2020.02033.
41. Ni L, Ye F, Cheng ML, et al. Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals. Immunity. 2020; 52(6):971-977.e3. https://doi.org/10.1016/j.immuni.2020.04.023.
42. Thevarajan I, Nguyen T, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nature medicine. 2020; 26(4):453-455. https://doi.org/10.1038/s41591-020-0819-2.
43. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. Journal of microbiology, immunology, and infection Wei mian yu gan ran za zhi. 2020; 53(3):368--370. https://doi.org/10.1016/j.jmii.2020.03.005.
44. Wong CK, Lam CW, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clinical and experimental immunology. 2004; 136(1):95-103. https://doi.org/10.1111/j.1365-2249.2004.02415.
45. Lau S, Lau C, Chan KH, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. The Journal of general virology. 2013; 94(Pt 12):2679-2690. https://doi.org/10.1099/vir.0.055533-0.
46. Zhou J, Chu H, Li C, et al. Active replication of Middle East respiratory syndrome coronavirus and aberrant induction of inflammatory cytokines and chemokines in human macrophages: implications for pathogenesis. The Journal of infectious diseases. 2014; 209(9):1331-1342. https://doi.org/10.1093/infdis/jit504.
47. Schreiber G. The Role of Type I Interferons in the Pathogenesis and Treatment of covid-19. Frontiers in immunology. 2020; 11:595739. https://doi.org/10.3389/fimmu.2020.595739.
48. Siracusano G, Pastori C, Lopalco L. Humoral Immune Responses in COVID-19 Patients: A Window on the State of the Art. Frontiers in immunology. 2020; 11:1049. https://doi.org/10.3389/fimmu.2020.01049.
49. Mo HY, Xu J, Ren XL, et al. Evaluation by indirect immunofluorescent assay and enzyme linked immunosorbent assay of the dynamic changes of serum antibody responses against severe acute respiratory syndrome coronavirus. Chinese medical journal. 2005; 118(6):446-450.
50. Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH. Disappearance of antibodies to SARS-associated coronavirus after recovery. The New England journal of medicine. 2007; 357(11):1162-1163. https://doi.org/10.1056/NEJMc070348.
51. Xiao AT, Gao C, Zhang S. Profile of specific antibodies to SARS-CoV-2: The first report. The Journal of infection. 2020; 81(1):147-178. https://doi.org/10.1016/j.jinf.2020.03.012.
52. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet. Infectious diseases. 2020; 20(5):565-574. https://doi.org/10.1016/S1473-3099(20)30196-1.
53. Shah VK, Firmal P, Alam A, et al. Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. Frontiers in immunology. 2020; 11:1949. https://doi.org/10.3389/fimmu.2020.01949.
54. Tan YJ, Goh PY, Fielding BC, et al. Profiles of antibody responses against severe acute respiratory syndrome coronavirus recombinant proteins and their potential use as diagnostic markers. Clinical and diagnostic laboratory immunology. 2004; 11(2):362-371. https://doi.org/10.1128/cdli.11.2.362-371.2004.
55. Meyer B, Drosten C, Müller MA. Serological assays for emerging coronaviruses: challenges and pitfalls. Virus research. 2014; 194:175-183. https://doi.org/10.1016/j.virusres.2014.03.018.
56. Wang Y, Zhang L, Sang L, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. The Journal of clinical investigation. 2020; 130(10):5235-5244. https://doi.org/10.1172/JCI138759.
57. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020; 71(15):778-785. https://doi.org/10.1093/cid/ciaa310.
58. Zhang Y, Xu J, Jia R, et al. Protective humoral immunity in SARS-CoV-2 infected pediatric patients. Cellular & molecular immunology. 2020; 17(7):768-770. https://doi.org/10.1038/s41423-020-0438-3.
59. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nature reviews. Immunology. 2020; 20(6):339-341. https://doi.org/10.1038/s41577-020-0321-6.
60. Karthik K, Senthilkumar T, Udhayavel S, et al. Role of antibody-dependent enhancement (ADE) in the virulence of SARS-CoV-2 and its mitigation strategies for the development of vaccines and immunotherapies to counter Covid-19. Human vaccines & immunotherapeutics. 2020; 16(12):3055-3060. https://doi.org/10.1080/21645515.2020.1796425.
61. Takada A, Kawaoka Y. Antibody-dependent enhancement of viral infection: molecular mechanisms and in vivo implications. Reviews in medical virology. 2003; 13(6):387-398. https://doi.org/10.1002/rmv.405.
62. Willey S, Aasa-Chapman MM, O'Farrell S, et al. Extensive complement-dependent enhancement of HIV-1 by autologous non-neutralising antibodies at early stages of infection. Retrovirology. 2011; 8:16. https://doi.org/10.1186/1742-4690-8-16.
63. Katzelnick LC, Gresh L, Halloran ME, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science (New York, N.Y.). 2017; 358(6365):929-932. https://doi.org/10.1126/science.aan6836.
64. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses?. Microbes and infection. 2020; 22(2):72-73. https://doi.org/10.1016/j.micinf.2020.02.006.
65. Tirado SM, Yoon KJ. Antibody-dependent enhancement of virus infection and disease. Viral immunology. 2003; 16(1):69-86.

https://doi.org/10.1089/088282403763635465.
66. Okba N, Müller MA, Li W, et al. Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease Patients. Emerging infectious diseases. 2020; 26(7):1478-1488. https://doi.org/10.3201/eid2607.200841.
67. Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nature medicine. 2020; 26(7):1033-1036. https://doi.org/10.1038/s41591-020-0913-5.
68. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet (London, England). 2020; 395(10223):473-475. https://doi.org/10.1016/S0140-6736(20)30317-2.
69. Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. Neuroimmunomodulation. 2002; 10(5):247-260. https://doi.org/10.1159/000069969.
70. Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, et al. Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. The European respiratory journal. 1999; 14(1):218-220. https://doi.org/10.1034/j.1399-3003.1999.14a37.x.
71. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. https://www.recoverytrial.net/fles/recovery_dexamethasone_statement_160620_v2final.pdf.
72. Villar, J. Ferrando, C. Martínez, D. et al. (2020). Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. The Lancet. Respiratory medicine. 1999; 8(3):267-276. https://doi.org/10.1016/S2213-2600(19)30417-5.
73. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. MedRxiv, 2020.
74. Papamanoli A, Yoo J, Grewal P, et al. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. European journal of clinical investigation. 2021; 51(2):e13458. https://doi.org/10.1111/eci.13458.
75. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. American journal of respiratory and critical care medicine. 2018; 197(6):757-767. https://doi.org/10.1164/rccm.201706-1172OC.
76. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS medicine. 2006; 3(9):e343. https://doi.org/10.1371/journal.pmed.0030343.
77. Sahraei Z, Shabani M, Shokouhi, S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. International journal of antimicrobial agents. 2020; 55(4):105945. https://doi.org/10.1016/j.ijantimicag.2020.105945.
78. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. International journal of antimicrobial agents. 2020; 55(5):105938. https://doi.org/10.1016/j.ijantimicag.2020.105938.
79. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. Clinical reviews in allergy & immunology. 2012; 42(2):145-153. https://doi.org/10.1007/s12016-010-8243-x.
80. Bonam SR, Muller S, Bayry J, et al. Autophagy as an emerging target for COVID-19: lessons from an old friend, chloroquine. Autophagy. 2020; 16(12):2260-2266. https://doi.org/10.1080/15548627.2020.1779467.
81. Lee SJ, Silverman E, Bargman JM. The role of antimalarial agents in the treatment of SLE and lupus nephritis. Nature reviews. Nephrology. 2011; 7(12):718-729. https://doi.org/10.1038/nrneph.2011.150.
82. Tang W, Cao Z, Han M, et. Al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ (Clinical research ed.). 2020; 369, m1849. https://doi.org/10.1136/bmj.m1849.
83. Savarino A, Boelaert JR, Cassone A, et. Al. Effects of chloroquine on viral infections: an old drug against today's diseases?. The Lancet. Infectious diseases. 2003' 3(11):722-727. https://doi.org/10.1016/s1473-3099(03)00806-5.
84. Vincent MJ, Bergeron E, Benjannet S, et. Al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virology journal. 2005; 2:69. https://doi.org/10.1186/1743-422X-2-69.
85. Zhonghua J, He HH, Xi ZZ, et. al. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Tuberc Respir Dis.. 2020; 43(3):185-8. https://pubmed.ncbi.nlm.nih.gov/32164085/.
86. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends. 2020; 14(1):72–73. https://doi.org/10.5582/bst.2020.01047.
87. Cuadrado-Lavín A, Olmos JM, Cifrian JM. et. al Controlled, double-blind, randomized trial to assess the efficacy and safety of hydroxychloroquine chemoprophylaxis in SARS CoV2 infection in healthcare personnel in the hospital setting: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21(1):472. https://doi.org/10.1186/s13063-020-04400-4.
88. Yao X, Ye F, Zhang M. et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020; 71(15):732–739. https://doi.org/10.1093/cid/ciaa237.
89. Rodriguez-Caruncho, C. & Bielsa Marsol, I. (2014). Antimalarials in dermatology: mechanism of action, indications, and side effects. Actas dermo-sifiliograficas, 105(3), 243–252. https://doi.org/10.1016/j.adengl.2012.10.021.
90. Jesus, A. A. & Goldbach-Mansky, R. (2014). IL-1 blockade in autoinflammatory syndromes. Annual review of medicine, 65, 223–244. https://doi.org/10.1146/annurev-med-061512-150641.

91. Monteagudo, L. A. Boothby, A. & Gertner, E. (2020). Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. ACR open rheumatology, 2(5), 276–282. https://doi.org/10.1002/acr2.11135.
92. Ruan, Q. Yang, K. Wang, W. et al. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine, 46(5), 846–848. https://doi.org/10.1007/s00134-020-05991-x.
93. Giavridis, T. van der Stegen, S. Eyquem, J. Hamieh, M. Piersigilli, A. & Sadelain, M. (2018). CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nature medicine, 24(6), 731–738. https://doi.org/10.1038/s41591-018-0041-7.
94. Shakoory, B. Carcillo, J. A. Chatham, W. W. et al. (2016). Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical care medicine, 44(2), 275–281. https://doi.org/10.1097/CCM.0000000000001402.
95. Huet, T. Beaussier, H. Voisin, O. (2020). Anakinra for severe forms of COVID-19: a cohort study. The Lancet. Rheumatology, 2(7), e393–e400. https://doi.org/10.1016/S2665-9913(20)30164-8.
96. Wohlford, G. F. Buckley, L. F. Vecchié, A. et al. (2020). Acute Effects of Interleukin-1 Blockade Using Anakinra in Patients With Acute Pericarditis. Journal of cardiovascular pharmacology, 76(1), 50–52. https://doi.org/10.1097/FJC.0000000000000847.
97. Lin, S. J. Kuo, M. L. Hsiao, H. S. & Lee, P. T. (2016). Azithromycin modulates immune response of human monocyte-derived dendritic cells and $CD4^+$ T cells. International immunopharmacology, 40, 318–326. https://doi.org/10.1016/j.intimp.2016.09.012.
98. Tyteca, D. Van Der Smissen, P. Mettlen, M. et al. (2002). Azithromycin, a lysosomotropic antibiotic, has distinct effects on fluid-phase and receptor-mediated endocytosis, but does not impair phagocytosis in J774 macrophages. Experimental cell research, 281(1), 86–100. https://doi.org/10.1006/excr.2002.5613.
99. Fantini, J. Chahinian, H. & Yahi, N. (2020). Synergistic antiviral effect of hydroxychloroquine and azithromycin in combination against SARS-CoV-2: What molecular dynamics studies of virus-host interactions reveal. International journal of antimicrobial agents, 56(2), 106020. https://doi.org/10.1016/j.ijantimicag.2020.106020.
100. Sandeep, S. & McGregor, K. (2020). Energetics Based Modeling of Hydroxychloroquine and Azithromycin Binding to the SARS-CoV-2 Spike (S) Protein-ACE2 Complex.
101. Touret, F. Gilles, M. Barral, K. et al. (2020). In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. Scientific reports, 10(1), 13093. https://doi.org/10.1038/s41598-020-70143-6.
102. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents. 2020; 56(1):105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.
103. Wambier CG. Focus on clinical outcomes of "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial". International journal of antimicrobial agents. 2021; 57(1):106175. https://doi.org/10.1016/j.ijantimicag.2020.106175.
104. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. 2020; 323(24):2493-2502. https://doi.org/10.1001/jama.2020.8630.
105. Chorin E, Wadhwani L, Magnani S. et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/ azithromycin. Heart rhythm. 2020; 17(9):1425-1433. https://doi.org/10.1016/j.hrthm.2020.05.014.
106. Gabay C, Emery P, van Vollenhoven R et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet (London, England). 2013; 381(9877):1541-1550. https://doi.org/10.1016/S0140-6736(13)60250-0.
107. Yokota S, Imagawa T, Mori M. et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet (London, England). 2008; 371(9617):998-1006. https://doi.org/10.1016/S0140-6736(08)60454-7.
108. Cao X. COVID-19: immunopathology and its implications for therapy. Nature reviews. Immunology. 2020; 20(5):269-270. https://doi.org/10.1038/s41577-020-0308-3.
109. Kaly L, Rosner I. Tocilizumab - a novel therapy for non-organ-specific autoimmune diseases. Best practice & research. Clinical rheumatology. 2012; 26(1):157-165. https://doi.org/10.1016/j.berh.2012.01.001.
110. Xu X, Han M, Li T. et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences of the United States of America. 2020; 117(20):10970–10975. https://doi.org/10.1073/pnas.2005615117.
111. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. Journal of medical virology. 2020; 92(7):814-818. https://doi.org/10.1002/jmv.25801.
112. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. The New England journal of medicine. 2020; 383(24):2333-2344. https://doi.org/10.1056/NEJMoa2028836.
113. Alzghari SK, Acuña VS. Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2020; 127:104380. https://doi.org/10.1016/j.jcv.2020.104380.
114. Puxeddu I, Caltran E, Rocchi V, et al. Hypersensitivity reactions during treatment with biological agents. Clinical and experimental rheumatology. 2016; 34(1):129-132.
115. Tchesnokov EP, Feng JY, Porter DP, Götte M. Mechanism of Inhibition of Ebola Virus RNA-

Dependent RNA Polymerase by Remdesivir. Viruses. 2019; 11(4):326. https://doi.org/10.3390/v11040326.
116. Hoenen T, Groseth A, Feldmann H. Therapeutic strategies to target the Ebola virus life cycle. Nature reviews. Microbiology. 2019; 17(10):593-606. https://doi.org/10.1038/s41579-019-0233-2.
117. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. The Journal of biological chemistry. 2020; 295(15):4773-4779. https://doi.org/10.1074/jbc.AC120.013056.
118. Agostini ML, Andres EL, Sims AC, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio. 2018; 9(2):e00221-18. https://doi.org/10.1128/mBio.00221-18.
119. Shih WJ, Yao C, Xie T. Data Monitoring for the Chinese Clinical Trials of Remdesivir in Treating Patients with COVID-19 During the Pandemic Crisis. Therapeutic innovation & regulatory science. 2020; 54(5):1236–1255. https://doi.org/10.1007/s43441-020-00159-7.
120. Wang Y, Zhou F, Zhang D, et al. Evaluation of the efficacy and safety of intravenous remdesivir in adult patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-controlled, multicentre trial. Trials. 2020; 21(1):422. https://doi.org/10.1186/s13063-020-04352-9.
121. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Science translational medicine. 2017; 9(396):eaal3653. https://doi.org/10.1126/scitranslmed.aal3653.
122. Goldman JD, Lye D, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. The New England journal of medicine. 2020; 383(19):1827-1837. https://doi.org/10.1056/NEJMoa2015301.
123. Porche DJ. Lopinavir/ritonavir. The Journal of the Association of Nurses in AIDS Care : JANAC. 2001; 12(2):101-104. https://doi.org/10.1016/S1055-3290(06)60137-4.
124. Cvetkovic RS, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. Drugs. 2003; 63(8):769–802. https://doi.org/10.2165/00003495-200363080-00004.
125. Rudin C, Burri M, Shen Y, et al. Long-term safety and effectiveness of ritonavir, nelfinavir, and lopinavir/ritonavir in antiretroviral-experienced HIV-infected children. The Pediatric infectious disease journal. 2008; 27(5):431-437. https://doi.org/10.1097/INF.0b013e3181646d5a.
126. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nature reviews. Drug discovery. 2020; 19(3):149-150. https://doi.org/10.1038/d41573-020-00016-0.
127. Chu CM, Cheng VC, Hung IF, et al.. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59(3):252–256. https://doi.org/10.1136/thorax.2003.012658.
128. Cao B, Wang Y, Wen D, Liu W. et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. The New England journal of medicine. 2020; 382(19):1787-1799. https://doi.org/10.1056/NEJMoa2001282.
129. Gérard A, Romani S, Fresse A. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. Therapie. 2020; 75(4):371-379. https://doi.org/10.1016/j.therap.2020.05.002.
130. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing, China). 2020; 6(10):119-1198. https://doi.org/10.1016/j.eng.2020.03.007.
131. Wu R, Wang L, Kuo HD et al. An Update on Current Therapeutic Drugs Treating COVID-19. Current pharmacology reports, 2020, 1–15. Advance online publication. https://doi.org/10.1007/s40495-020-00216-7
132. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Rawling M. Savory, E. & Stebbing, J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet (London, England). 2020; 395(10223):e30–e31. https://doi.org/10.1016/S0140-6736(20)30304-4.
133. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. The Journal of infection. 2020; 81(2):318–356. https://doi.org/10.1016/j.jinf.2020.04.017.
134. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. The Lancet. Infectious diseases. 2020; 20(4):400–402. https://doi.org/10.1016/S1473-3099(20)30132-8.
135. El Jammal, T Gerfaud-Valentin M, Sève P, Jamilloux, Y. Les inhibiteurs de JAK : perspectives pour la médecine interne [JAK inhibitors: Perspectives in internal medicine]. La Revue de medecine interne. 2019; 40(12):816-825. https://doi.org/10.1016/j.revmed.2019.07.016.
136. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral research, 2020, 178, 104791. https://doi.org/10.1016/j.antiviral.2020.104791.
137. Billiau A. The interferons: a brief introduction. The Medical clinics of North America, Suppl, 1986, 7–11. https://doi.org/10.1016/s0025-7125(16)36781-5.
138. Kalafateli M, Kourakli A, Gatselis N, Lambropoulou P. Thomopoulos K. Efficacy of Interferon A-2b Monotherapy in B-Thalassemics with Chronic Hepatitis C. Journal of Gastrointestinal & Liver Diseases. 2015; 24:2.
139. Hung IF, Lung KC, Tso EY. et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet (London, England). 2020; 395(10238):1695-1704. https://doi.org/10.1016/S0140-6736(20)31042-4.
140. Klok FA, Kruip M, Van Der Meer N. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research. 2020; 191:145-147. https://doi.org/10.1016/j.thromres.2020.04.013.
141. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients

with novel coronavirus pneumonia. Journal of thrombosis and haemostasis : JTH. 2020; 18(4):844-847. https://doi.org/10.1111/jth.14768.
142. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of thrombosis and haemostasis: JTH. 2020; 18(6):1421–1424. https://doi.org/10.1111/jth.14830.
143. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of thrombosis and haemostasis: JTH. 2020; 18(5):1094-1099. https://doi.org/10.1111/jth.14817.
144. Negri EM, Piloto BM, Morinaga LK, Jardim C, Lamy S, Ferreira MA, D'Amico EA et al. Heparin Therapy Improving Hypoxia in COVID-19 Patients - A Case Series. Frontiers in physiology. 2020; 11:573044. https://doi.org/10.3389/fphys.2020.573044.
145. Turshudzhyan A. Anticoagulation Options for Coronavirus Disease 2019 (COVID-19)-Induced Coagulopathy. Cureus. 2020; 12(5):e8150. https://doi.org/10.7759/cureus.8150.
146. Coppola A, Lombardi M, Tassoni MI, Carolla G, Tala M, Morandini R, Paoletti O, Testa S. COVID-19, thromboembolic risk and thromboprophylaxis: learning lessons from the bedside, awaiting evidence. Blood transfusion Trasfusione del sangue. 2020; 18(3):226-229. https://doi.org/10.2450/2020.0113-20.
147. Tiberghien P, de Lamballerie X, Morel P, Gallian P. Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how?. Vox sanguinis. 2020; 115(6):488-494. https://doi.org/10.1111/vox.12926.
148. Roback JD, Guarner J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. JAMA. 2020l; 323(16):1561-1562. https://doi.org/10.1001/jama.2020.4940.
149. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. The Journal of clinical investigation. 2020; 130(4):1545-1548. https://doi.org/10.1172/JCI138003.
150. Arabi Y, Balkhy H, Hajeer AH, et al. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springer Plus. 2015; 4:709. https://doi.org/10.1186/s40064-015-1490-9.
151. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2004; 10(7):676-678. https://doi.org/10.1111/j.1469-0691.2004.00956.x.
152. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020; 323(16):1582-1589. https://doi.org/10.1001/jama.2020.4783.
153. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. BMJ (Clinical research ed.). 2020; 369, m1375. https://doi.org/10.1136/bmj.m1375.
154. Fassett MJ, Lurvey LD, Yasumura L, et al. Universal SARS-Cov-2 Screening in Women Admitted for Delivery in a Large Managed Care Organization. American journal of perinatology. 2020; 37(11):111-1114. https://doi.org/10.1055/s-0040-1714060.
155. Umakanthan S, Chattu VK, Ranade AV, Das D, Basavarajegowda A, Bukelo M. A rapid review of recent advances in diagnosis, treatment and vaccination for COVID-19. AIMS public health. 2021; 8(1):137-153. https://doi.org/10.3934/publichealth.2021011.
156. Dicks MD, Spencer AJ, Edwards NJ, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. PloS one. 2012; 7(7):e40385. https://doi.org/10.1371/journal.pone.0040385.
157. Banerji A, Wickner PG, Saff R. et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. The journal of allergy and clinical immunology. In practice. 2020; S2213-2198(20)31411-2. Advance online publication. https://doi.org/10.1016/j.jaip.2020.12.047.
158. Oliver SE, Gargano JW, Marin M. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. MMWR. Morbidity and mortality weekly report. 2020; 69(50):1922-1924. https://doi.org/10.15585/mmwr.mm6950e2.
159. Polack FP, Thomas SJ, Kitchin N. et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. The New England journal of medicine. 2020; 383(27):2603–2615. https://doi.org/10.1056/NEJMoa2034577.