www.directivepublications.org

Journal of
Respiratory Medicine and Research

ISSN 2831-3240

Review Article

Aspects of immunopathology in humans during ssRNA virus infections - what do we know and do we have a foundation for treatment? - A narrative review - Part two.

Lars Lindberg[1]*, Jan Apelqvist[2]

[1]Institution of Clinical Sciences, PICU, Children's Hospital in Lund, Skane University Hospital, Lund University, Lasarettsgatan 48, S-221 85 Lund, Sweden.
[2]Institution of Clinical Sciences, Endocrinology, Skane University Hospital, S-214 28 Malmö, Sweden.

Abstract

Background: The pathophysiological mechanisms underlying single-stranded RNA (ssRNA) virus infections have been investigated extensively and at an accelerated pace in recent years, largely driven by the COVID-19 pandemic. Particular attention has been given to their potential roles in respiratory insufficiency, endothelial dysfunction, thrombosis, and inflammatory responses within the central nervous system.
Aim: This narrative review aims to summarize important pathophysiological mechanisms and pathways reported in the literature on respiratory ssRNA virus infections. Key findings are used to explain the outcome of present treatments and to suggest a more immuno-pathological based treatment strategy in these patients.
Method: The review is based on studies extracted from an extensive body of literature, encompassing basic research in biochemistry, immunology, virology, and genetics, as well as clinical and therapeutic studies, all indexed in the PubMed database.
Results: A species specific human immunological pathway reaction occurs against respiratory ssRNA viral genome antigen. It encompasses by an inferior interferon response limiting the force of the viral defense. A viral independent immunoinflammatory response, with monocytic cell infiltration in the lung ensues and may become severe, characterized by fortifying endothelial activation, a prothrombogenic pathway, and respiratory insufficiency. The pro-inflammatory response has potential ability of becoming chronic, with propagation to the central nervous system, but all responses seem potential treatable from an immune-pathological perspective.
Conclusion: The review may serve as a template for treatment and for future studies. It can be concluded that it is essential to have broad immunopathological knowledge when treating and developing strategies for ssRNA virus infections.

Keywords : *RNA virus, innate immunity, COVID-19, RSV, Influenza.*

Aspect of present therapies from immunopathological perspectives

(a) Antiviral drugs

Autopsy findings from patients who died of COVID-19 show that SARS-CoV-2 is non-cytotoxic and the associated respiratory injury is primarily caused by a concurrent virus-independent immunopathological process [53]. Consequently, antiviral treatment is expected to have limited efficacy, particularly in severely ill patients where the immune response is already activated. This has been demonstrated in several randomized, double-blind, placebo-controlled, multicenter trials, where the antiviral agent remdesivir did not result in significant clinical improvement in patients with moderate to severe COVID-19 [59, 211-213]. One randomized controlled trial (RCT) reported a reduction in time to recovery [214], while a European multicenter RCT found no clinical benefit from remdesivir treatment [215]. The limited or absent effect of remdesivir on all-cause or in-hospital mortality in patients with moderate to severe COVID-19 was later confirmed in the WHO Solidarity trial (including remdesivir and lopinavir) and in a Cochrane review on remdesivir for COVID-19 [60, 216]. These findings support the hypothesis that respiratory injury in COVID-19 is primarily immunologically mediated rather than due to direct viral cytotoxicity.

From a pathophysiologic perspective we assume that antiviral drugs may reduce viral load when administered early during infection, thereby limiting viral replication and mitigating

Corresponding Author:** **Lars Lindberg PhD,MD**, Associated professor, Institution of Clinical Sciences, PICU, Children's Hospital in Lund, Skane University Hospital, Lund University, Lasarettsgatan 48, S-221 85 Lund, Sweden. **Phone:** +46 70 569 86 84 ***Email: lars.lindberg@med.lu.se.
Orcid Id: 0000-0002-2246-2826.
Received: 05-Nov-2025, Manuscript No. JRMR - 5233**; Editor Assigned:** 07-Nov-2025 **; Reviewed:** 25-Nov-2025, QC No. JRMR - 5233 **; Published:** 03-Dec-2025, **DOI:** 10.52338/jrmr.2025.5233
Citation: **Lars Lindberg PhD,MD**. Aspects Of Immunopathology In Humans During Ssrna Virus Infections - What Do We Know And Do We Have A Foundation For Treatment? - A Narrative Review - Part Two. Journal of Respiratory Medicine and Research. 2025 December; 14(1). doi: 10.52338/jrmr.2025.5233.
Copyright © 2025 **Lars Lindberg PhD,MD**. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

the subsequent immune response. This was fortified in a meta-analysis on the effect of remdesivir where the authors concluded that a subgroup analysis of hospitalized patients with COVID-19 who did require low or no extra oxygen supplementation had a statistical significant reduced mortality [213]. Early treatment with oral antiviral drugs, such as nirmatrelvir/ritonavir (Paxlovid), in patients with mild to moderate COVID-19 was associated with a reduced risk of all-cause mortality. However, no significant effect was observed on the need for invasive mechanical ventilation, intensive care, or time to recovery in patients under 60 years of age or in vaccinated individuals, as reported in a retrospective cohort study [217]. A Cochrane systematic review concluded that there is very low-certainty evidence supporting an effect of Paxlovid on all-cause mortality, and currently, there is no conclusive evidence to support its use for preventing COVID-19 [218].

Similar findings have been described, when antiviral drugs have been studied in patients with other ssRNA viruses such as, RSV and influenza infections [219, 220].

In summary: The evidence for anti-viral treatment for respiratory ssRNA viruses is conflicting and most studies show no or only a marginal effect on all-cause mortality. Subgroup analyses indicate that there is a small, but statistical significant benefit of anti-viral treatment, if it is used early in patients with mild to moderate disease, thereby reducing the viral load and the following immune response.

(b) Anti-cytokine treatments

Infection with respiratory ssRNA viruses promotes an immunologic response characterized by production of various pro-inflammatory cytokines, chemokines, and adhesion molecules. T cells, neutrophils, and monocytes further amplify the inflammatory response through the release of additional pro-inflammatory mediators, as previously described.

Initially, these pro-inflammatory mediators were believed to cause or significantly contribute to multi-organ failure and mortality in COVID-19 patients [221]. The cytokine response to SARS-CoV-2 was characterized as a "cytokine storm," making cytokines a primary target for interventions aimed at reducing mortality [221-223]. However, subsequent findings revealed that the cytokine release was relatively modest. Interleukin-6 (IL-6) levels in COVID-19 patients were 10–200 times lower than those observed in patients with acute respiratory distress syndrome (ARDS) [224]. Conversely, the incidence of vasculitis with microthrombi was nine times higher in COVID-19 than in ARDS, suggesting that T cell-mediated endothelial activation (CD40L/CD40) played a more critical role than the cytokine release [225].

In addition, findings from autopsies and lung biopsies of patients with severe ssRNA virus infections suggest that tissue damage and ARDS-related mortality are primarily mediated by the recruitment and activation of monocytes and macrophages in the lungs, rather than by the presence of elevated pro-inflammatory mediators. These observations are supported by experimental studies, which demonstrated that inhibiting individual inflammatory mediators, or inducing hypocytokinemia in transgenic mice, failed to prevent the development of ARDS or reduce related mortality [226-228].

Several anti-cytokine treatments were recommended during the COVID-19 pandemic and numerous randomized controlled trials (RCTs) were initiated.

(i) Inhibition of IL-6

IL-6 levels increase during COVID-19 and have been implicated as a key mediator in the pro-inflammatory cascade. IL-6 exerts its effects through both a pro-inflammatory pathway, via its soluble receptor, and an anti-inflammatory pathway, via its membrane-bound receptor [229].

Tocilizumab, a monoclonal antibody targeting the IL-6 receptor initially demonstrated survival benefits in retrospective studies [230]. It was later recognized that retrospective studies frequently overestimated drug efficacy due to concurrent improvements in standard care over time and may have obscure the clinicians assessment of the drugs. This emphasized the need for blinded RCTs to accurately evaluate treatment effects. However, a randomized controlled trial comparing tocilizumab with standard care in severe COVID-19 was halted due to increased mortality of those treated with tocilizumab: 14 deaths (21%) occurred in the tocilizumab group versus 6 deaths (9%) in the standard care group [231]. Subsequent randomized, double-blind, placebo-controlled trials of tocilizumab in hospitalized COVID-19 patients showed no significant improvement in clinical status or mortality at either 28 or 60 days, even when combined with remdesivir [232-235]. In the large-scale RECOVERY trial, 4116 patients with hypoxia and elevated C-reactive protein levels were randomized to assess tocilizumab's effects. Tocilizumab was associated with reduced 28-day mortality (29%) compared to standard care (35%). However, subgroup analysis revealed that this benefit was limited to patients who also received glucocorticosteroids. In patients treated with tocilizumab alone, mortality was higher (39%) compared to standard care (35%), although the difference was not statistically significant, likely due to a smaller sample size [236]. This raises questions about the true efficacy of tocilizumab, suggesting that the observed mortality reduction may be attributable to corticosteroids rather than IL-6 inhibition alone.

Furthermore, sarilumab, another IL-6 receptor inhibitor, failed to demonstrate significant mortality benefits in a double-blind RCT involving patients with severe or critical COVID-19 [237] . Overall, most RCTs published to date have reported no or limited benefits of IL-6 inhibition with tocilizumab or sarilumab [238-241].

The efficacy of IL-6 inhibitors in COVID-19 remains uncertain and appears to depend on factors such as patient selection, timing of administration, and treatment protocols in the control groups. A consistent and substantial improvement in outcomes from IL-6 inhibition has not been confirmed in systematic reviews or meta-analyses [242].

(ii) Inhibition of IL-1 and IL18

Interleukin-1β (IL-1β) and interleukin-18 (IL-18) have been reported to be elevated in some studies of SARS-CoV-2 infection, suggesting an intense inflammatory activation [1, 243]. However, several other studies have found undetectable or normal IL-1β levels (<5 pg/mL), even in patients with severe disease or those who died [43, 46, 170, 244-252].

TLR8 responds to ssRNA viruses in humans by activating nuclear factor κB (NF-κB), a transcription factor for several cytokines including pro-IL-1β, and pro-IL-18 (IL-6, TNF-α, IL-12, IL-10). Pro-IL-1β and pro-IL-18 are inactive precursors that must be cleaved by caspase-1, an enzyme activated within a multiprotein complex known as the inflammasome to generate their active forms, IL-1β and IL-18.

The absence of IL-1β in many patients suggests that pro-IL-1β is not being cleaved or secreted during SARS-CoV-2 infection [43]. Although, inflammasome activation has been demonstrated in SARS-CoV-2-infected cells in vitro and ex vivo, but this process typically requires an additional external stimulus [247]. These findings suggest that while pro-IL-1β is induced, the inflammasome is not activated in vivo. Normal to low IL-1β levels in patients with COVID-19 and multisystem inflammatory syndrome in children (MIS-C) further support the lack of in vivo inflammasome activation [31, 32, 253].

Episodes of elevated IL-1β likely indicate secondary complications such as bacterial infections (pyroptosis) or tissue ischemia from thrombotic infarctions (apoptosis), both of which are known to activate the inflammasome. These complications may explain the cases where IL-1β elevation has been observed. Moreover, the absence of IL-1β activity suggests that neutrophil extracellular traps (NETs), which are linked to inflammasome activation, are unlikely to be a major factor. Additionally, retinoic acid-inducible gene I (RIG-I)-like receptors, which are RNA-sensing molecules involved in inflammasome activation, have been shown to be inhibited by ssRNA viruses such as SARS-CoV-2 and RSV [49, 254].

The lack of therapeutic efficacy in most randomized controlled trials involving IL-1 blockade in COVID-19 patients supports the conclusion that pro-IL-1β is not activated and that IL-1 is not a critical cytokine in SARS-CoV-2 infection (including COVID-19 and MIS-C) in the absence of complications [250, 252, 255].

Conversely, elevated free IL-18 levels in COVID-19 have been associated with an increased risk of macrophage activation syndrome (MAS), severity of illness, and higher mortality [169, 256, 257]. This may result from a caspase-1-independent activation pathway for pro-IL-18, which has been observed in human epithelial cells and macrophages. It explains the discrepancy between IL-1β and IL-18 levels [253, 258]. IL-18 is also known as an interferon-gamma (IFN-γ)-inducing factor and may account for the increased IFN-γ levels reported in COVID-19 and MIS-C [174, 259]. IL-18 stimulates IL-6 and GM-CSF. It also induces the release of an IL-18 binding protein, which controls the levels of the biological active free IL-18. Thereby, it induces a negative-feedback of its pro-inflammatory role [260]. IL-18 inhibition has been shown to effectively reverse IFN-γ-mediated symptoms, such as enterocolitis, rash (via CXCL9 release) [182] and thrombocytopenia—common features of MIS-C [261, 262].

(iii) Inhibition of tumor necrosis factor-alpha (TNF-α)

Elevated levels of TNF-α, IL-6 and IL-8, but not IL-1β have been shown to be associated with increased severity and mortality during SARS-CoV-2 infections [263]. The use of monoclonal antibodies inhibiting TNF-α have been investigated and the current evidence remains inconclusive with studies reporting conflicting results. A double-blind, placebo-controlled randomized controlled trial (RCT) found no statistically significant difference in outcomes between COVID-19 patients treated with infliximab and those receiving standard care [264]. However, a systematic review and meta-analysis indicated that early TNF-α inhibition was associated with a lower probability of hospitalization, although the search strategy and methodology was criticized [265, 266].

Combining infliximab with tocilizumab improved survival compared to treatment with tocilizumab and standard care alone in a prospective cohort study [267].

(iv) Inhibition of INF-γ

Lung biopsy studies in patients with COVID-19 have demonstrated a robust late IFN-γ activation, which correlates with disease severity, mortality, and the intensity of the inflammatory response [32, 167-169]. IFN-γ regulates the polarization and differentiation of macrophages toward the pro-inflammatory phenotype in the lungs. It is also increased during other ssRNA virus infections such as influenza [268]. Low levels of INF-γ were detected early in neonates, within 7 days after onset of RSV infections [269].

The INF-gamma (IFN-γ) signaling pathway can be inhibited using Janus kinase (JAK1/JAK2) inhibitors such as baricitinib, tofacitinib, and ruxolitinib. These agents possess anti-cytokine properties and can suppress the differentiation of monocytes into macrophages.

All three JAK inhibitors have been evaluated in randomized, placebo-controlled trials, showing beneficial efficacy on mortality and described as one of few proven treatments for patients with COVID-19 [270-273]. Several systematic

reviews and meta-analyses have also demonstrated that JAK inhibition is associated with a reduction in mortality among COVID-19 patients and a moderate- to high-certainty evidence to conclude that JAK inhibition is effective [274-277].

In summary, of the anti-cytokine treatments, inhibition of INF-γ proves to have the most consistent beneficial effect on outcome. Interestingly, it is also the cytokine that regulates the polarization of the recruited macrophages towards a pro-inflammatory direction in the lung.

(c) Glucocorticosteroids

Glucocorticosteroids bind to glucocorticoid receptors, which translocate into the cell nucleus and bind to glucocorticoid response elements in the promoter regions of target genes. This interaction leads to upregulation of anti-inflammatory proteins and/or downregulation of pro-inflammatory proteins. Glucocorticosteroids suppress NF-κB–mediated gene induction and limit the expression of several cytokines and chemokines, including IL-1 to IL-6, IL-8, IL-11, IL-13, IL-16, IFN-γ, GM-CSF, TNF-α, RANTES, eotaxin, macrophage inflammatory protein-1α, and monocyte chemoattractant protein-1. They also inhibit the induction of adhesion molecules such as ICAM-1 and VCAM-1 and reduce antibody synthesis [278, 279]

In a randomized, double-blinded controlled study in small children with acute RSV infection glucocorticosteroids treatment with dexamethasone had no effect on the course of the disease [280]. In another randomized, double-blind, placebo-controlled trial no beneficial effects could be detected by glucocorticosteroids treatment with dexamethasone in children with RSV infection needed mechanical ventilation [281].

In a review and meta-analysis evaluating the use of glucocorticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia no statistically significant difference was found between the treated group and control group [282].

In a controlled trial of hospitalized patients with COVID-19, glucocorticosteroid treatment with dexamethasone reduced 28-day all-cause mortality significantly, from 25.7% to 22.9%, with benefit confined only to patients with symptoms in more than 7 days and requiring respiratory support at randomization [283]. In those not receiving invasive mechanical ventilation at randomization the benefit was less and dexamethasone treatment decreased mortality from 22.7 % to 21.7 % (95 % - 0.84–1.03).

In the RECOVERY trial, treatment with the IL-6 inhibitor, tocilizumab, alone was associated with slightly higher mortality compared with patients who received standard care. However, glucocorticosteroids reversed this negative response to an insignificantly reduced mortality [236].

In summary, available data indicate that glucocorticosteroids may provide a small beneficial effect, although it remains unclear whether this benefit arises from a general anti-inflammatory activity or from inhibition of specific pro-inflammatory mediators. It indicates that the pro-inflammatory cells may be a more important target than the mediators they release.

(d) Inhibition of ANG II

Angiotensin II potentiates several pro-inflammatory responses and contributes to the polarization of the recruited macrophages to the pro-inflammatory M1 phenotype, one of the cell types responsible for the lung damages during ssRNA infection in the lung [284].

High circulating levels of ANG II have been associated with the severity of lung injury in patients with Influenza A infection, COVID-19, and acute respiratory distress syndrome (ARDS) [20, 24, 25, 147]. Administration of angiotensin-converting enzyme 2 (ACE2), which degrades ANG II, has been linked to reduced lung injury severity in ARDS [285], RSV [19], influenza A [21] and COVID19 [286]. Conditions associated with induction of ACE2 expression in the airways, such as during active smoking or estrogen therapy, have also been associated with a decreased risk of severe and fatal outcomes in patients with SARS-CoV-2 infection [138, 287, 288]. These findings support the role of ANG II in mediating lung injury during respiratory ssRNA viral infections.

Antihypertensive treatments that either inhibit ANG II production through ACE inhibitors or block the AT1R using angiotensin receptor blockers (ARBs) have been associated with improved outcomes in COVID-19 across numerous studies. ARBs, in particular, have been shown to reduce ICU admissions, the need for mechanical ventilation, hospital length of stay (LOS), and mortality, without increasing infection risk [289-303]. These improvements in patients with cardiovascular comorbidities suggest that ANG II and its AT1R play a pathogenic role in COVID-19-associated lung injury, as supported by experimental models [304].

The bioavailability and affinity for the AT1R in the lung may be of importance for ARBs lung protective effects. Telmisartan exhibits the highest distribution volume, lipophilicity, bioavailability, AT1R affinity, and the longest receptor dissociation half-life among tested ARBs. These properties make telmisartan particularly effective in sustaining AT1R inhibition [305-307]. Unlike losartan, telmisartan is not metabolized by cytochrome P450 enzymes, minimizing the risk of drug interactions [306]. Given the short half-life of ANG II (<1 minute) and its rapid internalization upon AT1R binding, sustained receptor blockade is likely beneficial.

Telmisartan significantly reduced 30-day mortality from 23% to 4% in multicenter RCT involving patients with severe COVID-19 [308]. Other ARBs with lower lung bioavailability and receptor affinity have shown more modest protective effects in large population studies of patients with COVID-19

and hypertension [297, 298, 300, 303, 309-311].

Meta-analyses and systematic reviews on the use of ACE inhibitors or ARBs have not consistently demonstrated a reduced risk of all-cause mortality, but an increased risk of acute kidney injury [312-314]. In severely ill patients, ARB use has been associated with decreased arterial blood pressure and increased need for vasopressor support [315]. This effect, often considered adverse, should instead be regarded as an expected pharmacological response in the context of a compensated hypovolemia. Inflammation-induced vascular leakage reduces circulating blood volume in severe COVID-19, and afterload-reducing effects by ARB´s may further lower arterial pressure unless intravascular volume is concurrently expanded using colloids or blood products. ARB´s do not impair cardiac contractility; however, compensating low blood pressure with vasopressors instead of volume resuscitation can compromise cardiac output, oxygen delivery, and renal perfusion, ultimately increasing morbidity [312, 316]. Optimal management involves supporting circulating volume with colloid solutions or blood products rather than crystalloids, which risk exacerbating interstitial fluid overload.

In summary, variability in ARB pharmacodynamics, dose, patient selection, timing of initiating treatment, and concurrent vasopressor use may influence clinical outcomes [316-318]. ARB therapy has not been associated with increased mortality [319]. While several trials have not shown statistically significant differences compared to placebo, often due to small sample sizes, ARBs have consistently demonstrated improvements in disease course.

(e) Stimulation of PPAR-γ

Several pharmacological agents enhance PPAR-γ expression, such as certain angiotensin receptor blockers (ARBs) and statins [306, 308, 318, 320-322]. Both have demonstrated protective effects in COVID-19 and promote the polarization of monocyte-derived macrophages toward the anti-inflammatory M2 phenotype. Among ARBs, telmisartan is a notably stronger PPAR-γ activator compared to candesartan, losartan, and other ARBs [306, 318, 323].

Other PPAR-γ agonists, such as melatonin and astaxanthin, have also been shown to be potential therapeutic agents for mitigating the hyper-inflammatory response in SARS-CoV-2 infection, RSV and influenza [185, 186, 324-327].

Notably, melatonin and its metabolites act as ligands for the PPAR-γ nuclear receptors at clinical concentrations. These molecules may exert effects through PPAR-γ activation, offering a mechanistic explanation for the previously observed cytoprotective effects of melatonin [328, 329]. Given their low toxicity, these compounds hold therapeutic promise for immune modulation and inflammatory resolution in ssRNA viral infection and other inflammatory diseases [327, 330, 331].

Plausible temporal phases of ssRNA viral infections, with aspects of current and future management strategies.

(a) The acute phase of ssRNA virus infections

A safe indoors distance from a ssRNA infected individual may require a range of at least 5–7 meters despite an air exchange rate of 10 times per hour and prevention from getting infection for caretakers may require the use of full-face, airtight gas masks. The effectiveness of infection control depends more on well-designed airflow patterns within a room than on the nominal air exchange rate [4].

The clinical course and treatment responses vary widely among individuals, influenced by factors such as pre-existing comorbidities, viral exposure load, genetic background, and ongoing therapies. To date, no treatment has proven curative. An important observation emerging from the COVID-19 pandemic is the significant improvement in standard care over time. This temporal improvement has, in some cases, exceeded the therapeutic impact of experimental treatments, complicating interpretation of retrospective studies [230, 231, 235, 240, 241, 332-335].

Vaccination remains by far the most effective strategy for reducing morbidity and mortality from ssRNA virus infections. Its prophylactic value is well established and irrefutably essential in public health.

When antiviral therapy is considered, it must be administered early in the disease course and targeted at high-risk individuals to effectively limit viral replication and reduce viral load. However, due to the high cost, antiviral drugs are often used as a last resort in severely ill patients—an approach that has proven ineffective in several randomized controlled trials [216]. The observed benefits of vaccination and early antiviral therapy suggest that, while ssRNA viruses may not be intrinsically cytotoxic, uncontrolled viral replication in the absence of inhibitory pathways (such as ACE2) can drive immune activation to life-threatening levels. This highlights the importance of early viral containment.

Findings from autopsies and lung biopsies of patients with severe ssRNA virus infections suggest that tissue damage and ARDS-related mortality are primarily mediated by the recruitment and activation of monocytes and macrophages in the lungs, rather than by the presence of elevated pro-inflammatory mediators. These observations are supported by experimental studies, which demonstrated that inhibiting individual inflammatory mediators, or inducing hypocytokinemia, failed to prevent the development of ARDS or reduce related mortality [226-228]. In contrast, treatments aimed at modulating the polarization and activation of pro-inflammatory monocytes that infiltrate the lung and produce inflammatory mediators have shown more promising results in both experimental models and clinical trials [226, 336].

Hypercytokinemia should be interpreted as a marker of immune cell activation, not as the direct cause of the lung injury. Therapies targeting macrophage activation and polarization, including ANG II inhibition, IFN-γ blockade, and PPAR-γ stimulation (e.g., with ARB or its agonist melatonin), have all been associated with reduced mortality in various studies. Even immunosuppression directed at the rapidly expanding monocyte population in critically ill patients has been advocated using topoisomerase I–II inhibitors, from both initial beneficial findings in clinical research and artificial intelligence–guided recommendations [336-341]. However, no single therapeutic agent appears sufficient to fully suppress the complex and multifactorial inflammatory pathways activated in response to ssRNA viruses. This suggests that coordinated, multi-agent treatment regimens, with minimal adverse effects, are required to effectively manage severe disease. For hospitalized or critically ill patients, interventions to prevent the polarization of recruited monocytes into pro-inflammatory macrophages seem to be essential. ARBs and PPAR-γ agonists (e.g. melatonin, statins) are low-cost, well-tolerated treatments that may serve this purpose effectively as first line therapies. The use of corticosteroids, aimed at suppressing the release of inflammatory mediators, has shown some clinical benefit when combined with other therapeutic strategies.

IFN-γ, a potent inducer of inducible nitric oxide synthase (iNOS), has been implicated in life-threatening complications and septic shock [172]. Its inhibition may represent a valuable next step in managing severely ill patients. Short-term therapy with topoisomerase II inhibitors (e.g., two-dose regimens) may also be considered as part of an escalated treatment strategy. To support infected cells production of the endogenously antiviral peptide - cathelicidin, by maintaining the vitamin D concentration, may also play a role in early prophylaxis. Vitamin D is activated and depleted during long lasting infections and maintaining adequate vitamin D levels has been associated with improved outcomes [205, 209, 342].

Due to the high frequency of arterial and venous thromboembolism despite thromboprophylaxis, antithrombin treatment should always be considered early in the course. Since the viral antigen can be long-lasting antithrombin treatment should not be stopped to early after the acute phase of illness [343, 344].

(b) The subacute phase and children with MIS-C

Children generally exhibit greater resilience to acute ssRNA virus infections compared to adults, with significantly lower morbidity and mortality. However, a subset of children develops difficulty in clearing the virus or its antigens, leading to the onset of multisystem inflammatory syndrome in children (MIS-C) [345]. This condition typically manifests 4–6 weeks after exposure to SARS-CoV-2, coinciding with the development and peak of the IgG immune response, which rises to active levels around 10–20 days and peaks between 20–30 days after infection onset [346]. MIS-C is characterized by a persistent fever lasting more than three days, accompanied by two or more clinical symptoms affecting various organ systems. Common manifestations include:

- Gastrointestinal symptoms: right-sided abdominal pain (62–92%), vomiting, or diarrhea.
- Cardiovascular involvement: varying degrees of hypotension (60–80%), and reduced cardiac contractility.
- Dermatologic and mucosal symptoms: rashes, conjunctivitis (74%), and mucosal changes.
- Hematologic abnormalities: signs of coagulopathy such as prolonged INR and aPTT, and elevated D-dimer levels.
- Respiratory symptoms: cough or dyspnea are present in 40–70% of cases.

Laboratory findings typically show elevated markers of inflammation and a positive history of SARS-CoV-2 exposure, confirmed by PCR or serology and [347].

Multiple inflammatory mediators are elevated during MIS-C, particularly IFN-γ and tumor necrosis factor-alpha (TNF-α) [173, 175, 252]. Notably, the gastrointestinal, dermatologic, and cardiovascular symptoms of MIS-C correspond with known effects of IFN-γ [169, 180, 182], which may serve as a clinical clue for its involvement. Given that MIS-C onset typically coincides with peak SARS-CoV-2-specific IgG levels and viral antigen persistency, one treatment option has focused on trying to block the interaction between the IgG-antigen complex and the Fc-γ receptors on the macrophages, thereby minimize the release of inflammatory mediators, such as TNF-α and INF-γ. This is achieved by administering high-dose intravenous immunoglobulin (IVIG), which binds to and block the Fc-γ receptors on the macrophages. IgG without antigenic content will not triggering cytokine release [348]. IVIG is usually combined with high-dose corticosteroids to further suppress inflammatory mediator release.

Since IFN-γ signals via Janus kinase (JAK) receptors, JAK inhibitors may represent a promising therapeutic option. Similarly, IL-18 inhibition, which is an IFN-γ inducing factor and reduce IFN-γ mediated symptoms, may be an attractive alternative [261, 262].

An interesting clinical observation is the consistently low or undetectable serum levels of vitamin D in patients with MIS-C (based on the author's experience from eight consecutive cases). Vitamin D deficiency may have impaired viral antigen elimination, thereby, contributing to sustained IgG-antigen exposure for the macrophages and an escalating inflammatory response and macrophage activation.

In contrast, IL-1β levels are typically low or within normal range in MIS-C, arguing against the use of IL-1 inhibition therapies such as anakinra in MIS-C [251, 252, 349].

For cases of IVIG- and steroid-resistant hyperinflammation—

particularly in the context of MIS-C, Kawasaki disease, hemophagocytic lymphohistiocytosis (HLH), or macrophage activation syndrome (MAS)—etoposide, a topoisomerase inhibitor, has demonstrated clinical efficacy by targeting and suppressing monocytic/macrophagic cell activation [339, 340, 350-352]. Short-term therapy (two doses) with a topoisomerase II inhibitor may offer a potential alternative therapeutic pathway in severe, refractory MIS-C cases not responding to IFN-γ inhibition.

(c) The chronic phase and the long COVID syndrome.

Approximately 2–3 months after infection with ssRNA viruses, a subset of patients develops a persistent post-viral fatigue syndrome. In the context of SARS-CoV-2, this condition—referred to as "long COVID"—occurs in over 10% of cases and persists for more than two months. Long COVID arises after the resolution of acute inflammation and peak immunoglobulin response, suggesting a link to ongoing activity in T cells and long lasting inflammatory response.

Symptoms are heterogeneous but primarily neurological, characterized by varying degrees of cognitive dysfunction. Common complaints include general malaise, intractable fatigue, memory impairment, and difficulty concentrating—collectively referred to as "brain fog." In severe cases, symptoms significantly impair activities of daily living [353]. Unlike vascular complications, long COVID does not typically present with paresis; rather, it is suggestive of inflammatory edema affecting cerebral signaling pathways. The syndrome shares features with other post-infectious syndromes such as chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) [354]. Although SARS-CoV-2 has been shown to disseminate throughout the body during acute infection, limited viral presence is found in the central nervous system (CNS), and no direct antiviral immune response has been observed in the CNS, arguing against direct viral cytotoxicity [53, 355]. Furthermore, there is no evidence of virus-induced structural brain damages. Nonetheless, autopsy findings from patients with acute COVID-19 have revealed neuro-inflammatory activation, including perivascular T-cell infiltration and widespread microglial activation, independent of viral antigen presence [354, 356].

Under normal conditions, microglial expression of the co-stimulatory molecule CD40 is low. During ssRNA virus infections the cytokines INF-γ and TNF-α significantly upregulate CD40 expression on microglia. These CD40+ microglia become highly responsive to CD40 ligand (CD40L) expressed on activated CD4+ T cells or present in its soluble form, leading to microglial release of pro-inflammatory mediators and chemokines [165, 194].

Neuro-inflammation mediated by activated microglia is a plausible mechanism underlying symptoms such as brain fog [357]. Elevated levels of the chemokine CCL11—linked to cognitive impairment—have also been observed in long COVID patients [357]. CCL11 appears to be released by the choroid plexus in association with T-cell infiltration and elevated IL-4 levels, the latter uniquely increased in long COVID [358].

CCL11 induces activated microglia to release reactive oxygen species (ROS), contributing to neuronal toxicity [359].

Patients with severe COVID-19 exhibit elevated levels of soluble CD40L and enhanced CD4+ T-cell activity, both of which can contribute to CD40-mediated microglial activation [84]. Activation of the CD40–CD40L axis in the brain disrupts the blood–brain barrier, induces cerebral edema, injures glial cells, and promotes microthrombosis [195]. It also initiates intracellular signaling cascades that increase the production of cytokines, chemokines, and neurotoxins, amplifying neuro-inflammation in the CNS [194]. These mechanisms are closely linked to the cognitive dysfunction, fatigue, and other nonspecific neurological symptoms seen in both ICU patients and those with long COVID [196, 197].

A persistent T-cell–mediated inflammatory response has also been documented in long COVID, possibly driven by limited viral replication in tissue reservoirs [360, 361].

This inability to fully eliminate the virus may also relate to vitamin D deficiency, which compromises cathelicidin production and the elimination of the virus. In fact, low serum 25(OH)D levels, particularly in patients with neurocognitive symptoms, were the only variable significantly associated with long COVID in a multivariate analysis [206].

Long COVID-19 is characterized by prolonged expression of CD40L on activated T cells, and this can activate microglial cells in the brain, similar to the mechanism that may underlie the therapeutic efficacy of monoclonal antibodies targeting CD40L in MS [362].

The CD40–CD40L pathway represents a critical immunological bridge between the immune system and the CNS and is recognized as a key factor in several neurological diseases [195]. Targeting this pathway has gained therapeutic interest following positive results from a phase 2 trial of frexalimab, a monoclonal antibody that blocks CD40–CD40L interaction, in MS [362].

Despite the compelling indication implicating the CD40–CD40L pathway in long COVID and its therapeutic potential, there are currently no known ongoing clinical studies investigating this target in the context of long COVID [360].

Conclusion

This narrative review, in two parts, analyzes and describes the immunopathological pathways involved in human infections caused by single-stranded RNA (ssRNA) viruses. These infections influence host immune responses in diverse ways and to varying degrees. A plausible pathophysiological course is proposed, outlining distinct temporal phases of the

disease. From a pathophysiological perspective, current and potential treatment strategies are discussed in relation to these mechanisms. Overall, it can be concluded that adopting a broad immunopathological perspective is essential when managing and developing therapeutic strategies for diseases caused by ssRNA viruses.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395(10223):497-506.

2. Kalil AC, Thomas PG: Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care 2019, 23(1):258.

3. Achaiah NC, Subbarajasetty SB, Shetty RM: R(0) and R(e) of COVID-19: Can We Predict When the Pandemic Outbreak will be Contained? Indian J Crit Care Med 2020, 24(11):1125-1127.

4. Kulkarni H, Smith CM, Lee Ddo H, Hirst RA, Easton AJ, O'Callaghan C: Evidence of Respiratory Syncytial Virus Spread by Aerosol. Time to Revisit Infection Control Strategies? Am J Respir Crit Care Med 2016, 194(3):308-316.

5. Graudenz GS, Degobbi C, Saldiva PH: SARS-CoV-2. Long Distance Airborne Transmission and its Public Health Implications. Clinics (Sao Paulo) 2020, 75:e2343.

6. Olsen SJ, Chang HL, Cheung TY, Tang AF, Fisk TL, Ooi SP, Kuo HW, Jiang DD, Chen KT, Lando J et al: Transmission of the severe acute respiratory syndrome on aircraft. N Engl J Med 2003, 349(25):2416-2422.

7. Dalskov L, Mohlenberg M, Thyrsted J, Blay-Cadanet J, Poulsen ET, Folkersen BH, Skaarup SH, Olagnier D, Reinert L, Enghild JJ et al: SARS-CoV-2 evades immune detection in alveolar macrophages. EMBO Rep 2020, 21(12):e51252.

8. Mercer J, Schelhaas M, Helenius A: Virus entry by endocytosis. Annu Rev Biochem 2010, 79:803-833.

9. Lakadamyali M, Rust MJ, Zhuang X: Endocytosis of influenza viruses. Microbes Infect 2004, 6(10):929-936.

10. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A et al: SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020, 181(2):271-280 e278.

11. Jackson CB, Farzan M, Chen B, Choe H: Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol 2022, 23(1):3-20.

12. Costa LB, Perez LG, Palmeira VA, Macedo ECT, Ribeiro VT, Lanza K, Simoes ESAC: Insights on SARS-CoV-2 Molecular Interactions With the Renin-Angiotensin System. Front Cell Dev Biol 2020, 8:559841.

13. Bayati A, Kumar R, Francis V, McPherson PS: SARS-CoV-2 infects cells after viral entry via clathrin-mediated endocytosis. J Biol Chem 2021, 296:100306.

14. Glebov OO: Understanding SARS-CoV-2 endocytosis for COVID-19 drug repurposing. FEBS J 2020, 287(17):3664-3671.

15. Song A, Phandthong R, Talbot P: Endocytosis inhibitors block SARS-CoV-2 pseudoparticle infection of mink lung epithelium. Front Microbiol 2023, 14:1258975.

16. Griffiths CD, Bilawchuk LM, McDonough JE, Jamieson KC, Elawar F, Cen Y, Duan W, Lin C, Song H, Casanova JL et al: IGF1R is an entry receptor for respiratory syncytial virus. Nature 2020, 583(7817):615-619.

17. Krzyzaniak MA, Zumstein MT, Gerez JA, Picotti P, Helenius A: Host cell entry of respiratory syncytial virus involves macropinocytosis followed by proteolytic activation of the F protein. PLoS Pathog 2013, 9(4):e1003309.

18. Battles MB, McLellan JS: Respiratory syncytial virus entry and how to block it. Nat Rev Microbiol 2019, 17(4):233-245.

19. Gu H, Xie Z, Li T, Zhang S, Lai C, Zhu P, Wang K, Han L, Duan Y, Zhao Z et al: Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep 2016, 6:19840.

20. Huang F, Guo J, Zou Z, Liu J, Cao B, Zhang S, Li H, Wang W, Sheng M, Liu S et al: Angiotensin II plasma levels are linked to disease severity and predict fatal outcomes in H7N9-infected patients. Nat Commun 2014, 5:3595.

21. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, Ju X, Liang Z, Liu Q, Zhao Y et al: Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 2014, 5:3594.

22. Ni Z, Wang J, Yu X, Wang Y, Wang J, He X, Li C, Deng G, Shi J, Kong H et al: Influenza virus uses mGluR2 as an endocytic receptor to enter cells. Nat Microbiol 2024, 9(7):1764-1777.

23. Rust MJ, Lakadamyali M, Zhang F, Zhuang X: Assembly of endocytic machinery around individual influenza viruses during viral entry. Nat Struct Mol Biol 2004, 11(6):567-573.

24. Liu NH, Y. Chen, R-G. Zhu, H-M.: High rate of increased level of plasma angiotensin II and its gender difference in ccovid-19: An analysis o f55 hospitalized patients with covid-19 in a single hospital, wuhan, China. J Clin Toxicol 2021, 11(S16):6.

25. Wu Z, Hu R, Zhang C, Ren W, Yu A, Zhou X: Elevation of plasma angiotensin II level is a potential pathogenesis for the critically ill COVID-19 patients. Crit Care 2020, 24(1):290.

26. Duan T, Du Y, Xing C, Wang HY, Wang RF: Toll-Like Receptor Signaling and Its Role in Cell-Mediated Immunity. Front Immunol 2022, 13:812774.

27. Bender AT, Tzvetkov E, Pereira A, Wu Y, Kasar S, Przetak MM, Vlach J, Niewold TB, Jensen MA, Okitsu SL: TLR7 and TLR8 Differentially Activate the IRF and NF-kappaB Pathways in Specific Cell Types to Promote Inflammation. Immunohorizons 2020, 4(2):93-107.

28. Martinez-Espinoza I, Guerrero-Plata A: The Relevance of TLR8 in Viral Infections. Pathogens 2022, 11(2).

29. Triantafilou K, Orthopoulos G, Vakakis E, Ahmed MA, Golenbock DT, Lepper PM, Triantafilou M: Human cardiac inflammatory responses triggered by Coxsackie B viruses are mainly Toll-like receptor (TLR) 8-dependent. Cell Microbiol 2005, 7(8):1117-1126.

30. Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, Lipford G, Wagner H, Bauer S: Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science 2004, 303(5663):1526-1529.

31. Campbell GR, To RK, Hanna J, Spector SA: SARS-CoV-2, SARS-CoV-1, and HIV-1 derived ssRNA sequences activate the NLRP3 inflammasome in human macrophages through a non-classical pathway. iScience 2021, 24(4):102295.

32. Desterke C, Turhan AG, Bennaceur-Griscelli A, Griscelli F: PPARgamma Cistrome Repression during Activation of Lung Monocyte-Macrophages in Severe COVID-19. iScience 2020, 23(10):101611.

33. Janke M, Poth J, Wimmenauer V, Giese T, Coch C, Barchet W, Schlee M, Hartmann G: Selective and direct activation of human neutrophils but not eosinophils by Toll-like receptor 8. J Allergy Clin Immunol 2009, 123(5):1026-1033.

34. Gorden KB, Gorski KS, Gibson SJ, Kedl RM, Kieper WC, Qiu X, Tomai MA, Alkan SS, Vasilakos JP: Synthetic TLR agonists reveal functional differences between human TLR7 and TLR8. J Immunol 2005, 174(3):1259-1268.

35. Tanji H, Ohto U, Shibata T, Taoka M, Yamauchi Y, Isobe T, Miyake K, Shimizu T: Toll-like receptor 8 senses degradation products of single-stranded RNA. Nat Struct Mol Biol 2015, 22(2):109-115.

36. Leiva-Juarez MM, Kolls JK, Evans SE: Lung epithelial cells: therapeutically inducible effectors of antimicrobial defense. Mucosal Immunol 2018, 11(1):21-34.

37. Gardiman E, Bianchetto-Aguilera F, Gasperini S, Tiberio L, Scandola M, Lotti V, Gibellini D, Salvi V, Bosisio D, Cassatella MA et al: SARS-CoV-2-Associated ssRNAs Activate Human Neutrophils in a TLR8-Dependent Fashion. Cells 2022, 11(23).

38. Saikh KU: MyD88 and beyond: a perspective on MyD88-targeted therapeutic approach for modulation of host immunity. Immunol Res 2021, 69(2):117-128.

39. Zhou S, Cerny AM, Fitzgerald KA, Kurt-Jones EA, Finberg RW: Role of interferon regulatory factor 7 in T cell responses during acute lymphocytic choriomeningitis virus infection. J Virol 2012, 86(20):11254-11265.

40. Badr G, Saad H, Waly H, Hassan K, Abdel-Tawab H, Alhazza IM, Ahmed EA: Type I interferon (IFN-alpha/beta) rescues B-lymphocytes from apoptosis via PI3Kdelta/Akt, Rho-A, NFkappaB and Bcl-2/Bcl(XL). Cell Immunol 2010, 263(1):31-40.

41. Menendez D, Snipe J, Marzec J, Innes CL, Polack FP, Caballero MT, Schurman SH, Kleeberger SR, Resnick MA: p53-responsive TLR8 SNP enhances human innate immune response to respiratory syncytial virus. J Clin Invest 2019, 129(11):4875-4884.

42. Zheng Y, Zhuang MW, Han L, Zhang J, Nan ML, Zhan P, Kang D, Liu X, Gao C, Wang PH: Severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. Signal Transduct Target Ther 2020, 5(1):299.

43. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, Pere H, Charbit B, Bondet V, Chenevier-Gobeaux C et al: Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020, 369(6504):718-724.

44. Reizis B: Plasmacytoid Dendritic Cells: Development, Regulation, and Function. Immunity 2019, 50(1):37-50.

45. Hattermann K, Picard S, Borgeat M, Leclerc P, Pouliot M, Borgeat P: The Toll-like receptor 7/8-ligand resiquimod (R-848) primes human neutrophils for leukotriene B4, prostaglandin E2 and platelet-activating factor biosynthesis. FASEB J 2007, 21(7):1575-1585.

46. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, Jordan TX, Oishi K, Panis M, Sachs D et al: Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell 2020, 181(5):1036-1045 e1039.

47. Yin X, Riva L, Pu Y, Martin-Sancho L, Kanamune J, Yamamoto Y, Sakai K, Gotoh S, Miorin L, De Jesus PD et al: MDA5 Governs the Innate Immune Response to SARS-CoV-2 in Lung Epithelial Cells. Cell Rep 2021, 34(2):108628.

48. Lee JY, Wing PAC, Gala DS, Noerenberg M, Jarvelin AI, Titlow J, Zhuang X, Palmalux N, Iselin L, Thompson MK et al: Absolute quantitation of individual SARS-CoV-2 RNA molecules provides a new paradigm for infection dynamics and variant differences. Elife 2022, 11.

49. Kimura S, Matsumiya T, Shiba Y, Nakanishi M, Hayakari R, Kawaguchi S, Yoshida H, Imaizumi T: The Essential Role of Double-Stranded RNA-Dependent Antiviral Signaling in the Degradation of Nonself Single-Stranded RNA in Nonimmune Cells. J Immunol 2018, 201(3):1044-1052.

50. Jain J, Gaur S, Chaudhary Y, Kaul R: The molecular biology of intracellular events during Coronavirus infection cycle. Virusdisease 2020, 31(2):75-79.

51. Channappanavar R, Zhao J, Perlman S: T cell-mediated immune response to respiratory coronaviruses. Immunol Res 2014, 59(1-3):118-128.

52. Welsh RM, Bahl K, Wang XZ: Apoptosis and loss of virus-specific CD8+ T-cell memory. Curr Opin Immunol 2004, 16(3):271-276.

53. Dorward DA, Russell CD, Um IH, Elshani M, Armstrong SD, Penrice-Randal R, Millar T, Lerpiniere CEB, Tagliavini G, Hartley CS et al: Tissue-Specific Immunopathology in Fatal COVID-19. Am J Respir Crit Care Med 2021, 203(2):192-201.

54. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, Frank S, Turek D, Willi N, Pargger H et al: Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020, 77(2):198-209.

55. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H: Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020, 395(10234):1417-1418.

56. Wang Z, Wang Y, Yan Q, Cai C, Feng Y, Huang Q, Li T, Yuan S, Huang J, Luo ZH et al: FPR1 signaling aberrantly regulates S100A8/A9 production by CD14(+)FCN1(hi) macrophages and aggravates pulmonary pathology in severe COVID-19. Commun Biol 2024, 7(1):1321.

57. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, Cheng L, Li J, Wang X, Wang F et al: Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med 2020, 26(6):842-844.

58. Jafarzadeh A, Chauhan P, Saha B, Jafarzadeh S, Nemati M: Contribution of monocytes and macrophages to the local tissue inflammation and cytokine storm in COVID-19: Lessons from SARS and MERS, and potential therapeutic interventions. Life Sci 2020, 257:118102.

59. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q et al: Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020, 395(10236):1569-1578.

60. Grundeis F, Ansems K, Dahms K, Thieme V, Metzendorf MI, Skoetz N, Benstoem C, Mikolajewska A, Griesel M, Fichtner F et al: Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev 2023, 1(1):CD014962.

61. Yang Y, Wang Y, Li L, Chen F, Zhang P: Activation of the Toll-like receptor 8 pathway increases the immunogenicity of mesenchymal stem cells from umbilical cord. Mol Med Rep 2017, 16(2):2061-2068.

62. Julia A, Bonafonte-Pardas I, Gomez A, Lopez-Lasanta M, Lopez-Corbeto M, Martinez-Mateu SH, Llados J, Rodriguez-Nunez I, Myers RM, Marsal S: Targeting of the CD80/86 proinflammatory axis as a therapeutic strategy to prevent severe COVID-19. Sci Rep 2021, 11(1):11462.

63. Lumsden JM, Roberts JM, Harris NL, Peach RJ, Ronchese F: Differential requirement for CD80 and CD80/CD86-dependent costimulation in the lung immune response to an influenza virus infection. J Immunol 2000, 164(1):79-85.

64. Fuse S, Obar JJ, Bellfy S, Leung EK, Zhang W, Usherwood EJ: CD80 and CD86 control antiviral CD8+ T-cell function and immune surveillance of murine gammaherpesvirus 68. J Virol 2006, 80(18):9159-9170.

65. Esensten JH, Helou YA, Chopra G, Weiss A, Bluestone JA: CD28 Costimulation: From Mechanism to Therapy. Immunity 2016, 44(5):973-988.

66. Linsley PS, Greene JL, Brady W, Bajorath J, Ledbetter JA, Peach R: Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors. Immunity 1994, 1(9):793-801.

67. Linsley PS, Ledbetter JA: The role of the CD28 receptor during T cell responses to antigen. Annu Rev Immunol 1993, 11:191-212.

68. Grewal IS, Flavell RA: The role of CD40 ligand in costimulation and T-cell activation. Immunol Rev 1996, 153:85-106.

69. Inwald DP, McDowall A, Peters MJ, Callard RE, Klein NJ: CD40 is constitutively expressed on platelets and provides a novel mechanism for platelet activation. Circ Res 2003, 92(9):1041-1048.

70. Takada YK, Shimoda M, Maverakis E, Felding BH, Cheng RH, Takada Y: Soluble CD40L activates soluble and cell-surface integrin alphavbeta3, alpha5beta1, and alpha4beta1 by binding to the allosteric ligand-binding site (site 2). J Biol Chem 2021, 296:100399.

71. Tang T, Cheng X, Truong B, Sun L, Yang X, Wang H: Molecular basis and therapeutic implications of CD40/CD40L immune checkpoint. Pharmacol Ther 2021, 219:107709.

72. Pamukcu B, Lip GY, Snezhitskiy V, Shantsila E: The CD40-CD40L system in cardiovascular disease. Ann Med 2011, 43(5):331-340.

73. Zhang B, Wu T, Chen M, Zhou Y, Yi D, Guo R: The CD40/CD40L system: a new therapeutic target for disease. Immunol Lett 2013, 153(1-2):58-61.

74. Davis B, Zou MH: CD40 ligand-dependent tyrosine nitration of prostacyclin synthase in vivo. Circulation 2005, 112(14):2184-2192.

75. Hausding M, Jurk K, Daub S, Kroller-Schon S, Stein J, Schwenk M, Oelze M, Mikhed Y, Kerahrodi JG, Kossmann S et al: CD40L contributes to angiotensin II-induced pro-thrombotic state, vascular inflammation, oxidative stress and endothelial dysfunction. Basic Res Cardiol 2013, 108(6):386.

76. Gavins FN, Li G, Russell J, Perretti M, Granger DN: Microvascular thrombosis and CD40/CD40L signaling. J Thromb Haemost 2011, 9(3):574-581.

77. Urban D, Thanabalasingam U, Stibenz D, Kaufmann J, Meyborg H, Fleck E, Grafe M, Stawowy P: CD40/CD40L interaction induces E-selectin dependent leukocyte adhesion to human endothelial cells and inhibits endothelial cell migration. Biochem Biophys Res Commun 2011, 404(1):448-452.

78. Kotowicz K, Dixon GL, Klein NJ, Peters MJ, Callard RE: Biological function of CD40 on human endothelial cells: costimulation with CD40 ligand and interleukin-4 selectively induces expression of vascular cell adhesion molecule-1 and P-selectin resulting in preferential adhesion of lymphocytes. Immunology 2000, 100(4):441-448.

79. Wu MD, Atkinson TM, Lindner JR: Platelets and von Willebrand factor in atherogenesis. Blood 2017, 129(11):1415-1419.

80. Tahir S, Wagner AH, Dietzel S, Mannell H, Pircher J, Weckbach LT, Hecker M, Pohl U: Endothelial CD40 Mediates Microvascular von Willebrand Factor-Dependent Platelet Adhesion Inducing Inflammatory Venothrombosis in ADAMTS13 Knockout Mice. Thromb Haemost 2020, 120(3):466-476.

81. Moller K, Adolph O, Grunow J, Elrod J, Popa M, Ghosh S, Schwarz M, Schwale C, Grassle S, Huck V et al: Mechanism and functional impact of CD40 ligand-induced von Willebrand factor release from endothelial cells. Thromb Haemost 2015, 113(5):1095-1108.

82. Henn V, Slupsky JR, Grafe M, Anagnostopoulos I, Forster R, Muller-Berghaus G, Kroczek RA: CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature 1998, 391(6667):591-594.

83. Matthies KM, Newman JL, Hodzic A, Wingett DG: Differential regulation of soluble and membrane CD40L proteins in T cells. Cell Immunol 2006, 241(1):47-58.

84. Philippe A, Chocron R, Bonnet G, Yatim N, Sutter W, Hadjadj J, Weizman O, Guerin CL, Mirault T, Fauvel C et al: Platelet activation and coronavirus disease 2019 mortality: Insights from coagulopathy, antiplatelet therapy and inflammation. Arch Cardiovasc Dis 2023, 116(4):183-191.

85. Lee N, Jeon K, Park MJ, Song W, Jeong S: Predicting survival in patients with SARS-CoV-2 based on cytokines and soluble immune checkpoint regulators. Front Cell Infect Microbiol 2024, 14:1397297.

86. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pao CRR, Righy C, Franco S, Souza TML, Kurtz P et al: Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020, 136(11):1330-1341.

87. Chakrabarti S, Rizvi M, Pathak D, Kirber MT, Freedman JE: Hypoxia influences CD40-CD40L mediated inflammation in endothelial and monocytic cells. Immunol Lett 2009, 122(2):170-184.

88. Senchenkova EY, Russell J, Vital SA, Yildirim A, Orr AW, Granger DN, Gavins FNE: A critical role for both CD40 and VLA5 in angiotensin II-mediated thrombosis and inflammation. FASEB J 2018, 32(6):3448-3456.

89. Al-Tamimi AO, Yusuf AM, Jayakumar MN, Ansari AW, Elhassan M, AbdulKarim F, Kannan M, Halwani R, Ahmad F: SARS-CoV-2 infection induces soluble platelet activation markers and PAI-1 in the early moderate stage of COVID-19. Int J Lab Hematol 2022, 44(4):712-721.

90. Senchenkova EY, Russell J, Esmon CT, Granger DN: Roles of Coagulation and fibrinolysis in angiotensin II-enhanced microvascular thrombosis. Microcirculation 2014, 21(5):401-407.

91. Vaughan DE, Lazos SA, Tong K: Angiotensin II regulates the expression of plasminogen activator inhibitor-1 in cultured endothelial cells. A potential link between the renin-angiotensin system and thrombosis. J Clin Invest 1995, 95(3):995-1001.

92. Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, Urban S, Nydam TL, Moore PK, McIntyre RC, Jr.: Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. J Am Coll Surg 2020, 231(2):193-203 e191.

93. Sakamoto T, Kudoh T, Sakamoto K, Matsui K, Ogawa H: Antithrombotic effects of losartan in patients with hypertension complicated by atrial fibrillation: 4A (Angiotensin II Antagonist of platelet Aggregation in patients with Atrial fibrillation), a pilot study. Hypertens Res 2014, 37(6):513-518.

94. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A et al: Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020.

95. Gu J, Xie Z, Gao Z, Liu J, Korteweg C, Ye J, Lau LT, Lu J, Gao Z, Zhang B et al: H5N1 infection of the respiratory tract and beyond: a molecular pathology study. Lancet 2007, 370(9593):1137-1145.

96. Shieh WJ, Blau DM, Denison AM, Deleon-Carnes M, Adem P, Bhatnagar J, Sumner J, Liu L, Patel M, Batten B et al: 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 2010, 177(1):166-175.

97. Short KR, Kuiken T, Van Riel D: Role of Endothelial Cells in the Pathogenesis of Influenza in Humans. J Infect Dis 2019, 220(11):1859-1860.

98. Short KR, Veldhuis Kroeze EJ, Reperant LA, Richard M, Kuiken T: Influenza virus and endothelial cells: a species specific relationship. Front Microbiol 2014, 5:653.

99. van den Berg J, Haslbauer JD, Stalder AK, Romanens A, Mertz KD, Studt JD, Siegemund M, Buser A, Holbro A, Tzankov A: Von Willebrand factor and the thrombophilia of severe COVID-19: in situ evidence from autopsies. Res Pract Thromb Haemost 2023, 7(4):100182.

100. Lim MS, McRae S: COVID-19 and immunothrombosis: Pathophysiology and therapeutic implications. Crit Rev Oncol Hematol 2021, 168:103529.

101. Cognasse F, Duchez AC, Audoux E, Ebermeyer T, Arthaud CA, Prier A, Eyraud MA, Mismetti P, Garraud O, Bertoletti L et al: Platelets as Key Factors in Inflammation: Focus on CD40L/CD40. Front Immunol 2022, 13:825892.

102. Ahmed S, Zimba O, Gasparyan AY: Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol 2020, 39(9):2529-2543.

103. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F et al: High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020.

104. Ten Cate H: Surviving Covid-19 with Heparin? N Engl J Med 2021, 385(9):845-846.

105. Silvin A, Chapuis N, Dunsmore G, Goubet AG, Dubuisson A, Derosa L, Almire C, Henon C, Kosmider O, Droin N et al: Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19. Cell 2020, 182(6):1401-1418 e1418.

106. Pruenster M, Kurz AR, Chung KJ, Cao-Ehlker X, Bieber S, Nussbaum CF, Bierschenk S, Eggersmann TK, Rohwedder I, Heinig K et al: Extracellular MRP8/14 is a regulator of beta2 integrin-dependent neutrophil slow rolling and adhesion. Nat Commun 2015, 6:6915.

107. Mahler M, Meroni PL, Infantino M, Buhler KA, Fritzler MJ: Circulating Calprotectin as a Biomarker of COVID-19 Severity. Expert Rev Clin Immunol 2021:1-13.

108. Zhang H, Zhang Q, Liu K, Yuan Z, Xu X, Dong J: Elevated level of circulating calprotectin correlates with severity and high mortality in patients with COVID-19. Immun Inflamm Dis 2024, 12(3):e1212.

109. Viemann D, Strey A, Janning A, Jurk K, Klimmek K, Vogl T, Hirono K, Ichida F, Foell D, Kehrel B et al: Myeloid-related proteins 8 and 14 induce a specific inflammatory response in human microvascular endothelial cells. Blood 2005, 105(7):2955-2962.

110. Barbosa MS, de Lima F, Peachazepi Moraes CR, Borba-Junior IT, Huber SC, Santos I, Bombassaro B, Dertkigil SSJ, Ilich A, Key NS et al: Angiopoietin2 is associated with coagulation activation and tissue factor expression in extracellular vesicles in COVID-19. Front Med (Lausanne) 2024, 11:1367544.

111. Pine AB, Meizlish ML, Goshua G, Chang CH, Zhang H, Bishai J, Bahel P, Patel A, Gbyli R, Kwan JM et al: Circulating markers of angiogenesis and endotheliopathy in COVID-19. Pulm Circ 2020, 10(4):2045894020966547.

112. Kaya T, Yaylaci S, Nalbant A, Yildirim I, Kocayigit H, Cokluk E, Sekeroglu MR, Koroglu M, Guclu E: Serum calprotectin as a novel biomarker for severity of COVID-19 disease. Ir J Med Sci 2021.

113. Zhao Y, Kilian C, Turner JE, Bosurgi L, Roedl K, Bartsch P, Gnirck AC, Cortesi F, Schultheiss C, Hellmig M et al: Clonal expansion and activation of tissue-resident memory-like Th17 cells expressing GM-CSF in the lungs of severe COVID-19 patients. Sci Immunol 2021, 6(56).

114. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, Sun R, Tian Z, Xu X, Wei H: Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl Sci Rev 2020, 7(6):998-1002.

115. Kawaguchi M, Kokubu F, Huang SK, Homma T, Odaka M, Watanabe S, Suzuki S, Ieki K, Matsukura S, Kurokawa M et al: The IL-17F signaling pathway is involved in the induction of IFN-gamma-inducible protein 10 in bronchial epithelial cells. J Allergy Clin Immunol 2007, 119(6):1408-1414.

116. Zaid Y, Dore E, Dubuc I, Archambault AS, Flamand O, Laviolette M, Flamand N, Boilard E, Flamand L: Chemokines and eicosanoids fuel the hyperinflammation within the lungs of patients with severe COVID-19. J Allergy Clin Immunol 2021, 148(2):368-380 e363.

117. McDyer JF, Goletz TJ, Thomas E, June CH, Seder RA: CD40 ligand/CD40 stimulation regulates the production of IFN-gamma from human peripheral blood mononuclear cells in an IL-12- and/or CD28-dependent manner. J Immunol 1998, 160(4):1701-1707.

118. Grant RA, Morales-Nebreda L, Markov NS, Swaminathan S, Querrey M, Guzman ER, Abbott DA, Donnelly HK, Donayre A, Goldberg IA et al: Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Nature 2021, 590(7847):635-641.

119. Bain CC, MacDonald AS: The impact of the lung environment on macrophage development, activation

and function: diversity in the face of adversity. Mucosal Immunol 2022, 15(2):223-234.

120. Allen JE, Ruckerl D: The Silent Undertakers: Macrophages Programmed for Efferocytosis. Immunity 2017, 47(5):810-812.

121. Yang XF, Wang H, Huang Y, Huang JH, Ren HL, Xu Q, Su XM, Wang AM, Ren F, Zhou MS: Myeloid Angiotensin II Type 1 Receptor Mediates Macrophage Polarization and Promotes Vascular Injury in DOCA/Salt Hypertensive Mice. Front Pharmacol 2022, 13:879693.

122. Yao M, Li M, Peng D, Wang Y, Li S, Zhang D, Yang B, Qiu HJ, Li LF: Unraveling Macrophage Polarization: Functions, Mechanisms, and "Double-Edged Sword" Roles in Host Antiviral Immune Responses. Int J Mol Sci 2024, 25(22).

123. Schmit T, Guo K, Tripathi JK, Wang Z, McGregor B, Klomp M, Ambigapathy G, Mathur R, Hur J, Pichichero M et al: Interferon-gamma promotes monocyte-mediated lung injury during influenza infection. Cell Rep 2022, 38(9):110456.

124. Mezouar S, Mege JL: Monitoring Macrophage Polarization in Infectious Disease, Lesson From SARS-CoV-2 Infection. Rev Med Virol 2025, 35(3):e70034.

125. Wang X, Zhang H, Ge Y, Cao L, He Y, Sun G, Jia S, Ma A, Liu J, Rong D et al: AT1R Regulates Macrophage Polarization Through YAP and Regulates Aortic Dissection Incidence. Front Physiol 2021, 12:644903.

126. Rostam HM, Reynolds PM, Alexander MR, Gadegaard N, Ghaemmaghami AM: Image based Machine Learning for identification of macrophage subsets. Sci Rep 2017, 7(1):3521.

127. Kossmann S, Schwenk M, Hausding M, Karbach SH, Schmidgen MI, Brandt M, Knorr M, Hu H, Kroller-Schon S, Schonfelder T et al: Angiotensin II-induced vascular dysfunction depends on interferon-gamma-driven immune cell recruitment and mutual activation of monocytes and NK-cells. Arterioscler Thromb Vasc Biol 2013, 33(6):1313-1319.

128. Ge Z, Chen Y, Ma L, Hu F, Xie L: Macrophage polarization and its impact on idiopathic pulmonary fibrosis. Front Immunol 2024, 15:1444964.

129. Capettini LS, Montecucco F, Mach F, Stergiopulos N, Santos RA, da Silva RF: Role of renin-angiotensin system in inflammation, immunity and aging. Curr Pharm Des 2012, 18(7):963-970.

130. Hoj Nielsen A, Knudsen F: Angiotensinogen is an acute-phase protein in man. Scand J Clin Lab Invest 1987, 47(2):175-178.

131. Ng KK, Vane JR: Conversion of angiotensin I to angiotensin II. Nature 1967, 216(5117):762-766.

132. Maranduca MA, Vamesu CG, Tanase DM, Clim A, Drochioi IC, Pinzariu AC, Filip N, Dima N, Tudorancea I, Serban DN et al: The RAAS Axis and SARS-CoV-2: From Oral to Systemic Manifestations. Medicina (Kaunas) 2022, 58(12).

133. van Kats JP, de Lannoy LM, Jan Danser AH, van Meegen JR, Verdouw PD, Schalekamp MA: Angiotensin II type 1 (AT1) receptor-mediated accumulation of angiotensin II in tissues and its intracellular half-life in vivo. Hypertension 1997, 30(1 Pt 1):42-49.

134. Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, Scalia R, Eguchi S: Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. Physiol Rev 2018, 98(3):1627-1738.

135. Garcia B, Zarbock A, Bellomo R, Legrand M: The alternative renin-angiotensin system in critically ill patients: pathophysiology and therapeutic implications. Crit Care 2023, 27(1):453.

136. Mizutani S, Ishii M, Hattori A, Nomura S, Numaguchi Y, Tsujimoto M, Kobayshi H, Murohara T, Wright JW: New insights into the importance of aminopeptidase A in hypertension. Heart Fail Rev 2008, 13(3):273-284.

137. Saponaro F, Rutigliano G, Sestito S, Bandini L, Storti B, Bizzarri R, Zucchi R: ACE2 in the Era of SARS-CoV-2: Controversies and Novel Perspectives. Front Mol Biosci 2020, 7:588618.

138. Zhang H, Rostami MR, Leopold PL, Mezey JG, O'Beirne SL, Strulovici-Barel Y, Crystal RG: Expression of the SARS-CoV-2 ACE2 Receptor in the Human Airway Epithelium. Am J Respir Crit Care Med 2020, 202(2):219-229.

139. Liu X, Yang N, Tang J, Liu S, Luo D, Duan Q, Wang X: Downregulation of angiotensin-converting enzyme 2 by the neuraminidase protein of influenza A (H1N1) virus. Virus Res 2014, 185:64-71.

140. Yang P, Gu H, Zhao Z, Wang W, Cao B, Lai C, Yang X, Zhang L, Duan Y, Zhang S et al: Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci Rep 2014, 4:7027.

141. Kintscher U, Slagman A, Domenig O, Rohle R, Konietschke F, Poglitsch M, Mockel M: Plasma Angiotensin Peptide Profiling and ACE (Angiotensin-Converting Enzyme)-2 Activity in COVID-19 Patients Treated With Pharmacological Blockers of the Renin-Angiotensin System. Hypertension 2020, 76(5):e34-e36.

142. Rieder M, Wirth L, Pollmeier L, Jeserich M, Goller I, Baldus N, Schmid B, Busch HJ, Hofmann M, Kern W et al: Serum ACE-2, angiotensin II, and aldosterone levels are unchanged in patients with COVID-19. Am J Hypertens 2020.

143. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW: Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 1994, 74(6):1141-1148.

144. Schieffer B, Luchtefeld M, Braun S, Hilfiker A, Hilfiker-Kleiner D, Drexler H: Role of NAD(P)H oxidase in angiotensin II-induced JAK/STAT signaling and cytokine induction. Circ Res 2000, 87(12):1195-1201.

145. Xu DF, Liu YJ, Mao YF, Wang Y, Xu CF, Zhu XY, Jiang L: Elevated angiotensin II induces platelet apoptosis through promoting oxidative stress in an AT1R-dependent manner during sepsis. J Cell Mol Med 2021, 25(8):4124-4135.

146. Zhang H, Schmeisser A, Garlichs CD, Plotze K, Damme U, Mugge A, Daniel WG: Angiotensin II-induced superoxide anion generation in human vascular endothelial cells: role of membrane-bound NADH-/NADPH-oxidases. Cardiovasc Res 1999, 44(1):215-222.

147. Parikh SM, Mammoto T, Schultz A, Yuan HT, Christiani D, Karumanchi SA, Sukhatme VP: Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. PLoS Med 2006, 3(3):e46.

148. Bodor C, Nagy JP, Vegh B, Nemeth A, Jenei A, MirzaHosseini S, Sebe A, Rosivall L: Angiotensin II increases the permeability and PV-1 expression of endothelial cells. Am J Physiol Cell Physiol 2012, 302(1):C267-276.

149. Benigni A, Cassis P, Remuzzi G: Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med 2010, 2(7):247-257.

150. Maranduca MA, Cosovanu MA, Clim A, Pinzariu AC, Filip N, Drochioi IC, Vlasceanu VI, Timofte DV, Nemteanu R, Plesa A et al: The Renin-Angiotensin System: The Challenge behind Autoimmune Dermatological Diseases. Diagnostics (Basel) 2023, 13(22).

151. Tham DM, Martin-McNulty B, Wang YX, Wilson DW, Vergona R, Sullivan ME, Dole W, Rutledge JC: Angiotensin II is associated with activation of NF-kappaB-mediated genes and downregulation of PPARs. Physiol Genomics 2002, 11(1):21-30.

152. de Queiroz TM, Lakkappa N, Lazartigues E: ADAM17-Mediated Shedding of Inflammatory Cytokines in Hypertension. Front Pharmacol 2020, 11:1154.

153. Obama T, Takayanagi T, Kobayashi T, Bourne AM, Elliott KJ, Charbonneau M, Dubois CM, Eguchi S: Vascular induction of a disintegrin and metalloprotease 17 by angiotensin II through hypoxia inducible factor 1alpha. Am J Hypertens 2015, 28(1):10-14.

154. Lumbers ER, Head R, Smith GR, Delforce SJ, Jarrott B, J HM, Pringle KG: The interacting physiology of COVID-19 and the renin-angiotensin-aldosterone system: Key agents for treatment. Pharmacol Res Perspect 2022, 10(1):e00917.

155. Maruyama R, Hatta E, Yasuda K, Smith NC, Levi R: Angiotensin-converting enzyme-independent angiotensin formation in a human model of myocardial ischemia: modulation of norepinephrine release by angiotensin type 1 and angiotensin type 2 receptors. J Pharmacol Exp Ther 2000, 294(1):248-254.

156. Lin YJ, Kwok CF, Juan CC, Hsu YP, Shih KC, Chen CC, Ho LT: Angiotensin II enhances endothelin-1-induced vasoconstriction through upregulating endothelin type A receptor. Biochem Biophys Res Commun 2014, 451(2):263-269.

157. Sandgren JA, Linggonegoro DW, Zhang SY, Sapouckey SA, Claflin KE, Pearson NA, Leidinger MR, Pierce GL, Santillan MK, Gibson-Corley KN et al: Angiotensin AT(1A) receptors expressed in vasopressin-producing cells of the supraoptic nucleus contribute to osmotic control of vasopressin. Am J Physiol Regul Integr Comp Physiol 2018, 314(6):R770-R780.

158. Fredlund P, Saltman S, Catt KJ: Aldosterone production

by isolated adrenal glomerulosa cells: stimulation by physiological concentrations of angiotensin II. Endocrinology 1975, 97(6):1577-1586.

159. Gupta D, Kumar A, Mandloi A, Shenoy V: Renin angiotensin aldosterone system in pulmonary fibrosis: Pathogenesis to therapeutic possibilities. Pharmacol Res 2021, 174:105924.

160. Uhal BD, Li X, Piasecki CC, Molina-Molina M: Angiotensin signalling in pulmonary fibrosis. Int J Biochem Cell Biol 2012, 44(3):465-468.

161. Wang J, Chen L, Chen B, Meliton A, Liu SQ, Shi Y, Liu T, Deb DK, Solway J, Li YC: Chronic Activation of the Renin-Angiotensin System Induces Lung Fibrosis. Sci Rep 2015, 5:15561.

162. Hu X, Ivashkiv LB: Cross-regulation of signaling pathways by interferon-gamma: implications for immune responses and autoimmune diseases. Immunity 2009, 31(4):539-550.

163. Jorgovanovic D, Song M, Wang L, Zhang Y: Roles of IFN-gamma in tumor progression and regression: a review. Biomark Res 2020, 8:49.

164. Kiritsy MC, Ankley LM, Trombley J, Huizinga GP, Lord AE, Orning P, Elling R, Fitzgerald KA, Olive AJ: A genetic screen in macrophages identifies new regulators of IFNgamma-inducible MHCII that contribute to T cell activation. Elife 2021, 10.

165. D'Aversa TG, Weidenheim KM, Berman JW: CD40-CD40L interactions induce chemokine expression by human microglia: implications for human immunodeficiency virus encephalitis and multiple sclerosis. Am J Pathol 2002, 160(2):559-567.

166. Nathan CF, Murray HW, Wiebe ME, Rubin BY: Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. J Exp Med 1983, 158(3):670-689.

167. Gadotti AC, de Castro Deus M, Telles JP, Wind R, Goes M, Garcia Charello Ossoski R, de Padua AM, de Noronha L, Moreno-Amaral A, Baena CP et al: IFN-gamma is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. Virus Res 2020, 289:198171.

168. Galbraith MD, Kinning KT, Sullivan KD, Araya P, Smith KP, Granrath RE, Shaw JR, Baxter R, Jordan KR, Russell S et al: Specialized interferon action in COVID-19. Proc Natl Acad Sci U S A 2022, 119(11).

169. Karki R, Sharma BR, Tuladhar S, Williams EP, Zalduondo L, Samir P, Zheng M, Sundaram B, Banoth B, Malireddi RKS et al: Synergism of TNF-alpha and IFN-gamma Triggers Inflammatory Cell Death, Tissue Damage, and Mortality in SARS-CoV-2 Infection and Cytokine Shock Syndromes. Cell 2021, 184(1):149-168 e117.

170. Merad M, Martin JC: Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020, 20(6):355-362.

171. Karupiah G, Xie QW, Buller RM, Nathan C, Duarte C, MacMicking JD: Inhibition of viral replication by interferon-gamma-induced nitric oxide synthase. Science 1993, 261(5127):1445-1448.

172. Kirkeboen KA, Strand OA: The role of nitric oxide in sepsis--an overview. Acta Anaesthesiol Scand 1999, 43(3):275-288.

173. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, Lee JH, Jasen C, Balamuth F, Barrett DM et al: Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest 2020, 130(11):5967-5975.

174. Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumado V, Fortuny C, Rios-Barnes M, Sanchez-de-Toledo J, Girona-Alarcon M, Mosquera JM et al: Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. J Clin Invest 2021, 131(6).

175. Diorio C, Shraim R, Vella LA, Giles JR, Baxter AE, Oldridge DA, Canna SW, Henrickson SE, McNerney KO, Balamuth F et al: Proteomic profiling of MIS-C patients indicates heterogeneity relating to interferon gamma dysregulation and vascular endothelial dysfunction. Nat Commun 2021, 12(1):7222.

176. Zoller EE, Lykens JE, Terrell CE, Aliberti J, Filipovich AH, Henson PM, Jordan MB: Hemophagocytosis causes a consumptive anemia of inflammation. J Exp Med 2011, 208(6):1203-1214.

177. Langer V, Vivi E, Regensburger D, Winkler TH, Waldner MJ, Rath T, Schmid B, Skottke L, Lee S, Jeon NL et

al: IFN-gamma drives inflammatory bowel disease pathogenesis through VE-cadherin-directed vascular barrier disruption. J Clin Invest 2019, 129(11):4691-4707.

178. Ito R, Shin-Ya M, Kishida T, Urano A, Takada R, Sakagami J, Imanishi J, Kita M, Ueda Y, Iwakura Y et al: Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice. Clin Exp Immunol 2006, 146(2):330-338.

179. Brasseit J, Kwong Chung CKC, Noti M, Zysset D, Hoheisel-Dickgreber N, Genitsch V, Corazza N, Mueller C: Divergent Roles of Interferon-gamma and Innate Lymphoid Cells in Innate and Adaptive Immune Cell-Mediated Intestinal Inflammation. Front Immunol 2018, 9:23.

180. Eriguchi Y, Nakamura K, Yokoi Y, Sugimoto R, Takahashi S, Hashimoto D, Teshima T, Ayabe T, Selsted ME, Ouellette AJ: Essential role of IFN-gamma in T cell-associated intestinal inflammation. JCI Insight 2018, 3(18).

181. Wang F, Schwarz BT, Graham WV, Wang Y, Su L, Clayburgh DR, Abraham C, Turner JR: IFN-gamma-induced TNFR2 expression is required for TNF-dependent intestinal epithelial barrier dysfunction. Gastroenterology 2006, 131(4):1153-1163.

182. Han JH, Suh CH, Jung JY, Ahn MH, Han MH, Kwon JE, Yim H, Kim HA: Elevated circulating levels of the interferon-gamma-induced chemokines are associated with disease activity and cutaneous manifestations in adult-onset Still's disease. Sci Rep 2017, 7:46652.

183. Croasdell A, Duffney PF, Kim N, Lacy SH, Sime PJ, Phipps RP: PPARgamma and the Innate Immune System Mediate the Resolution of Inflammation. PPAR Res 2015, 2015:549691.

184. Bouhlel MA, Derudas B, Rigamonti E, Dievart R, Brozek J, Haulon S, Zawadzki C, Jude B, Torpier G, Marx N et al: PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. Cell Metab 2007, 6(2):137-143.

185. Hasankhani A, Bahrami A, Tavakoli-Far B, Iranshahi S, Ghaemi F, Akbarizadeh MR, Amin AH, Abedi Kiasari B, Mohammadzadeh Shabestari A: The role of peroxisome proliferator-activated receptors in the modulation of hyperinflammation induced by SARS-CoV-2 infection: A perspective for COVID-19 therapy. Front Immunol 2023, 14:1127358.

186. Huang S, Zhu B, Cheon IS, Goplen NP, Jiang L, Zhang R, Peebles RS, Mack M, Kaplan MH, Limper AH et al: PPAR-gamma in Macrophages Limits Pulmonary Inflammation and Promotes Host Recovery following Respiratory Viral Infection. J Virol 2019, 93(9).

187. Li H, Jiang T, Li MQ, Zheng XL, Zhao GJ: Transcriptional Regulation of Macrophages Polarization by MicroRNAs. Front Immunol 2018, 9:1175.

188. Asada K, Sasaki S, Suda T, Chida K, Nakamura H: Antiinflammatory roles of peroxisome proliferator-activated receptor gamma in human alveolar macrophages. Am J Respir Crit Care Med 2004, 169(2):195-200.

189. Sibille Y, Reynolds HY: Macrophages and polymorphonuclear neutrophils in lung defense and injury. Am Rev Respir Dis 1990, 141(2):471-501.

190. Keikha R, Hashemi-Shahri SM, Jebali A: The miRNA neuroinflammatory biomarkers in COVID-19 patients with different severity of illness. Neurologia 2023, 38(6):e41-e51.

191. Zhang H, Alford T, Liu S, Zhou D, Wang J: Influenza virus causes lung immunopathology through down-regulating PPARgamma activity in macrophages. Front Immunol 2022, 13:958801.

192. Alexis JD, Wang N, Che W, Lerner-Marmarosh N, Sahni A, Korshunov VA, Zou Y, Ding B, Yan C, Berk BC et al: Bcr kinase activation by angiotensin II inhibits peroxisome-proliferator-activated receptor gamma transcriptional activity in vascular smooth muscle cells. Circ Res 2009, 104(1):69-78.

193. Nguyen VT, Benveniste EN: Critical role of tumor necrosis factor-alpha and NF-kappa B in interferon-gamma -induced CD40 expression in microglia/macrophages. J Biol Chem 2002, 277(16):13796-13803.

194. Chen K, Huang J, Gong W, Zhang L, Yu P, Wang JM: CD40/CD40L dyad in the inflammatory and immune responses in the central nervous system. Cell Mol Immunol 2006, 3(3):163-169.

195. Ots HD, Tracz JA, Vinokuroff KE, Musto AE: CD40-CD40L in Neurological Disease. Int J Mol Sci 2022, 23(8).

196. Hampshire A, Azor A, Atchison C, Trender W, Hellyer PJ, Giunchiglia V, Husain M, Cooke GS, Cooper E, Lound A

et al: Cognition and Memory after Covid-19 in a Large Community Sample. N Engl J Med 2024, 390(9):806-818.

197. Barrett TJ, Lee AH, Xia Y, Lin LH, Black M, Cotzia P, Hochman J, Berger JS: Platelet and Vascular Biomarkers Associate With Thrombosis and Death in Coronavirus Disease. Circ Res 2020, 127(7):945-947.

198. Campbell GR, Spector SA: Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response that inhibits human immunodeficiency virus type 1. PLoS Pathog 2012, 8(11):e1003017.

199. Chung C, Silwal P, Kim I, Modlin RL, Jo EK: Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection. Immune Netw 2020, 20(2):e12.

200. Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, Pohl J, Davidson DJ, Donis RO: Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS One 2011, 6(10):e25333.

201. Currie SM, Gwyer Findlay E, McFarlane AJ, Fitch PM, Bottcher B, Colegrave N, Paras A, Jozwik A, Chiu C, Schwarze J et al: Cathelicidins Have Direct Antiviral Activity against Respiratory Syncytial Virus In Vitro and Protective Function In Vivo in Mice and Humans. J Immunol 2016, 196(6):2699-2710.

202. Sousa FH, Casanova V, Findlay F, Stevens C, Svoboda P, Pohl J, Proudfoot L, Barlow PG: Cathelicidins display conserved direct antiviral activity towards rhinovirus. Peptides 2017, 95:76-83.

203. Akbar MR, Wibowo A, Pranata R, Setiabudiawan B: Low Serum 25-hydroxyvitamin D (Vitamin D) Level Is Associated With Susceptibility to COVID-19, Severity, and Mortality: A Systematic Review and Meta-Analysis. Front Nutr 2021, 8:660420.

204. Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL, Rovers M, Bont L: Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics 2011, 127(6):e1513-1520.

205. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP: Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 2020, 12(4).

206. di Filippo L, Frara S, Nannipieri F, Cotellessa A, Locatelli M, Rovere Querini P, Giustina A: Low Vitamin D Levels Are Associated With Long COVID Syndrome in COVID-19 Survivors. J Clin Endocrinol Metab 2023, 108(10):e1106-e1116.

207. Landry RL, Embers ME: The Probable Infectious Origin of Multiple Sclerosis. NeuroSci 2023, 4(3):211-234.

208. Siddiqui M, Manansala JS, Abdulrahman HA, Nasrallah GK, Smatti MK, Younes N, Althani AA, Yassine HM: Immune Modulatory Effects of Vitamin D on Viral Infections. Nutrients 2020, 12(9).

209. Benskin LL: A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is Increased in Vitamin D Deficiency. Front Public Health 2020, 8:513.

210. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA: Serum 25(OH)D Level on Hospital Admission Associated With COVID-19 Stage and Mortality. Am J Clin Pathol 2020.

211. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG et al: Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020, 383(19):1827-1837.

212. Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A et al: Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020, 324(11):1048-1057.

213. Amstutz A, Speich B, Mentre F, Rueegg CS, Belhadi D, Assoumou L, Burdet C, Murthy S, Dodd LE, Wang Y et al: Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med 2023, 11(5):453-464.

214. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S et al: Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020, 383(19):1813-1826.

215. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, Diallo A, Le MP, Peytavin G, Staub T et al: Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a

phase 3, randomised, controlled, open-label trial. Lancet Infect Dis 2022, 22(2):209-221.

216. Consortium WHOST, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernandez Garcia C, Kieny MP et al: Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2021, 384(6):497-511.

217. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM: Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. Lancet Infect Dis 2022, 22(12):1681-1693.

218. Reis S, Metzendorf MI, Kuehn R, Popp M, Gagyor I, Kranke P, Meybohm P, Skoetz N, Weibel S: Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. Cochrane Database Syst Rev 2023, 11(11):CD015395.

219. Clements CM, Carpenter CR, University ACPJCETaM: In nonsevere influenza, antiviral drugs do not reduce mortality or hospital admissions; some shorten symptom duration. Ann Intern Med 2025, 178(5):JC51.

220. Zou G, Cao S, Gao Z, Yie J, Wu JZ: Current state and challenges in respiratory syncytial virus drug discovery and development. Antiviral Res 2024, 221:105791.

221. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R: The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol 2020, 11:1446.

222. Rowaiye AB, Okpalefe OA, Onuh Adejoke O, Ogidigo JO, Hannah Oladipo O, Ogu AC, Oli AN, Olofinase S, Onyekwere O, Rabiu Abubakar A et al: Attenuating the Effects of Novel COVID-19 (SARS-CoV-2) Infection-Induced Cytokine Storm and the Implications. J Inflamm Res 2021, 14:1487-1510.

223. Ruan Q, Yang K, Wang W, Jiang L, Song J: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020, 46(5):846-848.

224. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO et al: Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med 2020, 8(12):1233-1244.

225. Sinha P, Matthay MA, Calfee CS: Is a "Cytokine Storm" Relevant to COVID-19? JAMA Intern Med 2020, 180(9):1152-1154.

226. Aoyagi T, Sato Y, Toyama M, Oshima K, Kawakami K, Kaku M: Etoposide and Corticosteroid Combination Therapy Improves Acute Respiratory Distress Syndrome in Mice. Shock 2019, 52(1):83-91.

227. Droebner K, Reiling SJ, Planz O: Role of hypercytokinemia in NF-kappaB p50-deficient mice after H5N1 influenza A virus infection. J Virol 2008, 82(22):11461-11466.

228. Salomon R, Hoffmann E, Webster RG: Inhibition of the cytokine response does not protect against lethal H5N1 influenza infection. Proc Natl Acad Sci U S A 2007, 104(30):12479-12481.

229. Reeh H, Rudolph N, Billing U, Christen H, Streif S, Bullinger E, Schliemann-Bullinger M, Findeisen R, Schaper F, Huber HJ et al: Response to IL-6 trans- and IL-6 classic signalling is determined by the ratio of the IL-6 receptor alpha to gp130 expression: fusing experimental insights and dynamic modelling. Cell Commun Signal 2019, 17(1):46.

230. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, Cossi S: Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med 2020, 76:31-35.

231. Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LCP et al: Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021, 372:n84.

232. Rosas IO: Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. MedRxiv 2020.

233. Rosas IO, Brau N, Waters M, Go RC, Malhotra A, Hunter BD, Bhagani S, Skiest D, Savic S, Douglas IS et al: Tocilizumab in patients hospitalised with COVID-19 pneumonia: Efficacy, safety, viral clearance, and antibody response from a randomised controlled trial (COVACTA). EClinicalMedicine 2022, 47:101409.

234. Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, Cavalcante AW, Overcash JS, Hanania

NA, Skarbnik A et al: Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med 2021, 47(11):1258-1270.

235. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, Bruzzi P, Boni F, Braglia L, Turra C et al: Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2021, 181(1):24-31.

236. Group RC: Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021, 397(10285):1637-1645.

237. Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, Patel N, Hagino O, Sarilumab C-GSG: Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021, 9(5):522-532.

238. McCreary EK, Meyer NJ: Covid-19 controversies: the tocilizumab chapter. BMJ 2021, 372:n244.

239. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L et al: Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021, 384(1):20-30.

240. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM et al: Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med 2020, 383(24):2333-2344.

241. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, Group C-C: Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2021, 181(1):32-40.

242. Chen CX, Hu F, Wei J, Yuan LT, Wen TM, Gale RP, Liang Y: Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19). Leukemia 2021, 35(6):1661-1670.

243. Zhao N, Di B, Xu LL: The NLRP3 inflammasome and COVID-19: Activation, pathogenesis and therapeutic strategies. Cytokine Growth Factor Rev 2021, 61:2-15.

244. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H et al: Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020, 130(5):2620-2629.

245. Del Valle DM, Kim-Schulze S, Hsin-Hui H, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz T, Madduri D, Stock A et al: An inflammatory cytokine signature helps predict COVID-19 severity and death. medRxiv 2020.

246. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B et al: Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 2020, 584(7821):463-469.

247. Varchetta S, Mele D, Oliviero B, Mantovani S, Ludovisi S, Cerino A, Bruno R, Castelli A, Mosconi M, Vecchia M et al: Unique immunological profile in patients with COVID-19. Cell Mol Immunol 2021, 18(3):604-612.

248. Waltuch T, Gill P, Zinns LE, Whitney R, Tokarski J, Tsung JW, Sanders JE: Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department. Am J Emerg Med 2020, 38(10):2246 e2243-2246 e2246.

249. Jia F, Wang G, Xu J, Long J, Deng F, Jiang W: Role of tumor necrosis factor-alpha in the mortality of hospitalized patients with severe and critical COVID-19 pneumonia. Aging (Albany NY) 2021, 13(21):23895-23912.

250. Gurlevik SL, Ozsurekci Y, Sag E, Derin Oygar P, Kesici S, Akca UK, Cuceoglu MK, Basaran O, Goncu S, Karakaya J et al: The difference of the inflammatory milieu in MIS-C and severe COVID-19. Pediatr Res 2022, 92(6):1805-1814.

251. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, Gillen JK, Perez MM, Soshnick SH, Conway EE, Jr. et al: Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (MIS-C): A Multi-institutional Study from New York City. J Pediatr 2020, 224:24-29.

252. Ravichandran S, Tang J, Grubbs G, Lee Y, Pourhashemi S, Hussaini L, Lapp SA, Jerris RC, Singh V, Chahroudi A et al: SARS-CoV-2 immune repertoire in MIS-C and pediatric COVID-19. Nat Immunol 2021, 22(11):1452-1464.

253. Rodrigues TS, de Sa KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, Goncalves AV, Perucello DB, Andrade WA, Castro R et al: Inflammasomes are activated in response

to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med 2021, 218(3).

254. Onomoto K, Onoguchi K, Yoneyama M: Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors. Cell Mol Immunol 2021, 18(3):539-555.

255. group C-C: Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med 2021, 9(3):295-304.

256. Kerget B, Kerget F, Aksakal A, Askin S, Saglam L, Akgun M: Evaluation of alpha defensin, IL-1 receptor antagonist, and IL-18 levels in COVID-19 patients with macrophage activation syndrome and acute respiratory distress syndrome. J Med Virol 2021, 93(4):2090-2098.

257. Nasser SMT, Rana AA, Doffinger R, Kafizas A, Khan TA, Nasser S: Elevated free interleukin-18 associated with severity and mortality in prospective cohort study of 206 hospitalised COVID-19 patients. Intensive Care Med Exp 2023, 11(1):9.

258. Sugawara S, Uehara A, Nochi T, Yamaguchi T, Ueda H, Sugiyama A, Hanzawa K, Kumagai K, Okamura H, Takada H: Neutrophil proteinase 3-mediated induction of bioactive IL-18 secretion by human oral epithelial cells. J Immunol 2001, 167(11):6568-6575.

259. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F et al: Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 2020, 9(1):1123-1130.

260. Marino L, Criniti A, Guida S, Bucci T, Ballesio L, Suppa M, Galardo G, Vacca A, Santulli M, Angeloni A et al: Interleukin 18 and IL-18 BP response to Sars-CoV-2 virus infection. Clin Exp Med 2023, 23(4):1243-1250.

261. Canna SW, Girard C, Malle L, de Jesus A, Romberg N, Kelsen J, Surrey LF, Russo P, Sleight A, Schiffrin E et al: Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. J Allergy Clin Immunol 2017, 139(5):1698-1701.

262. Li S, Jiang L, Beckmann K, Hojen JF, Pessara U, Powers NE, de Graaf DM, Azam T, Lindenberger J, Eisenmesser EZ et al: A novel anti-human IL-1R7 antibody reduces IL-18-mediated inflammatory signaling. J Biol Chem 2021, 296:100630.

263. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A et al: An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 2020, 26(10):1636-1643.

264. O'Halloran JA, Ko ER, Anstrom KJ, Kedar E, McCarthy MW, Panettieri RA, Jr., Maillo M, Nunez PS, Lachiewicz AM, Gonzalez C et al: Abatacept, Cenicriviroc, or Infliximab for Treatment of Adults Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA 2023, 330(4):328-339.

265. Kokkotis G, Kitsou K, Bamias G: Letter: COVID-19 outcomes and anti-TNF treatments-comprehensive evidence matters. Authors' reply. Aliment Pharmacol Ther 2022, 55(9):1235-1236.

266. Kokkotis G, Kitsou K, Xynogalas I, Spoulou V, Magiorkinis G, Trontzas I, Trontzas P, Poulakou G, Syrigos K, Bamias G: Systematic review with meta-analysis: COVID-19 outcomes in patients receiving anti-TNF treatments. Aliment Pharmacol Ther 2022, 55(2):154-167.

267. Sarhan NM, Warda AEA, Ibrahim HSG, Schaalan MF, Fathy SM: Evaluation of infliximab/tocilizumab versus tocilizumab among COVID-19 patients with cytokine storm syndrome. Sci Rep 2023, 13(1):6456.

268. Califano D, Furuya Y, Roberts S, Avram D, McKenzie ANJ, Metzger DW: IFN-gamma increases susceptibility to influenza A infection through suppression of group II innate lymphoid cells. Mucosal Immunol 2018, 11(1):209-219.

269. Aberle JH, Aberle SW, Rebhandl W, Pracher E, Kundi M, Popow-Kraupp T: Decreased interferon-gamma response in respiratory syncytial virus compared to other respiratory viral infections in infants. Clin Exp Immunol 2004, 137(1):146-150.

270. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S et al: Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med 2021, 384(9):795-807.

271. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, Piruzeli MLB, Goldman JD, Alatorre-Alexander J, de Cassia Pellegrini R et al: Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase

3 trial. Lancet Respir Med 2021, 9(12):1407-1418.

272. Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, Kalil Filho R, Junior VM, Soeiro AM, Tognon AP et al: Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021.

273. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Huang L, Wang N et al: Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol 2020, 146(1):137-146 e133.

274. Manoharan S, Ying LY: Does baricitinib reduce mortality and disease progression in SARS-CoV-2 virus infected patients? A systematic review and meta analysis. Respir Med 2022, 202:106986.

275. Limen RY, Sedono R, Sugiarto A, Hariyanto TI: Janus kinase (JAK)-inhibitors and coronavirus disease 2019 (Covid-19) outcomes: a systematic review and meta-analysis. Expert Rev Anti Infect Ther 2022, 20(3):425-434.

276. Kow CS, Ramachandram DS, Hasan SS: Effect of JAK Inhibitors on the Risk of Death in Patients with Moderate to Severe COVID-19: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can J Hosp Pharm 2024, 77(2):e3493.

277. Kramer A, Prinz C, Fichtner F, Fischer AL, Thieme V, Grundeis F, Spagl M, Seeber C, Piechotta V, Metzendorf MI et al: Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev 2022, 6(6):CD015209.

278. Leung DY, Bloom JW: Update on glucocorticoid action and resistance. J Allergy Clin Immunol 2003, 111(1):3-22; quiz 23.

279. Williams DM: Clinical Pharmacology of Corticosteroids. Respir Care 2018, 63(6):655-670.

280. Buckingham SC, Jafri HS, Bush AJ, Carubelli CM, Sheeran P, Hardy RD, Ottolini MG, Ramilo O, DeVincenzo JP: A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: effects on RSV quantity and clinical outcome. J Infect Dis 2002, 185(9):1222-1228.

281. van Woensel JB, Vyas H, Group ST: Dexamethasone in children mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus: a randomized controlled trial. Crit Care Med 2011, 39(7):1779-1783.

282. Zhou Y, Fu X, Liu X, Huang C, Tian G, Ding C, Wu J, Lan L, Yang S: Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. Sci Rep 2020, 10(1):3044.

283. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A et al: Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med 2020.

284. Lv K, Liang Q: Macrophages in sepsis-induced acute lung injury: exosomal modulation and therapeutic potential. Front Immunol 2024, 15:1518008.

285. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H et al: Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005, 436(7047):112-116.

286. Zoufaly A, Poglitsch M, Aberle JH, Hoepler W, Seitz T, Traugott M, Grieb A, Pawelka E, Laferl H, Wenisch C et al: Human recombinant soluble ACE2 in severe COVID-19. Lancet Respir Med 2020, 8(11):1154-1158.

287. Seeland U, Coluzzi F, Simmaco M, Mura C, Bourne PE, Heiland M, Preissner R, Preissner S: Evidence for treatment with estradiol for women with SARS-CoV-2 infection. BMC Med 2020, 18(1):369.

288. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P et al: Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020, 584(7821):430-436.

289. Banwait R, Singh D, Blanco A, Rastogi V, Abusaada K: Renin-Angiotensin-Aldosterone System Blockers Prior to Hospitalization and Their Association With Clinical Outcomes in Coronavirus Disease 2019 (COVID-19). Cureus 2021, 13(2):e13429.

290. Baral R, Tsampasian V, Debski M, Moran B, Garg P, Clark A, Vassiliou VS: Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA Netw Open 2021, 4(3):e213594.

291. Choksi TT, Zhang H, Chen T, Malhotra N: Outcomes of Hospitalized COVID-19 Patients Receiving Renin

Angiotensin System Blockers and Calcium Channel Blockers. Am J Nephrol 2021, 52(3):250-260.

292. Guo X, Zhu Y, Hong Y: Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension: A Meta-Analysis. Hypertension 2020, 76(2):e13-e14.

293. Hamada S, Suzuki T, Tokuda Y, Taniguchi K, Shibuya K: Comparing clinical outcomes of ARB and ACEi in patients hospitalized for acute COVID-19. Sci Rep 2023, 13(1):11810.

294. Li S, Sarangarajan R, Jun T, Kao YH, Wang Z, Hao K, Schadt E, Kiebish MA, Granger E, Narain NR et al: In-hospital use of ACE inhibitors/angiotensin receptor blockers associates with COVID-19 outcomes in African American patients. J Clin Invest 2021, 131(19).

295. Macedo AVS, de Barros ESPGM, de Paula TC, Moll-Bernardes RJ, Mendonca Dos Santos T, Mazza L, Feldman A, Arruda G, de Albuquerque DC, de Sousa AS et al: Discontinuing vs continuing ACEIs and ARBs in hospitalized patients with COVID-19 according to disease severity: Insights from the BRACE CORONA trial. Am Heart J 2022, 249:86-97.

296. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G: Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. N Engl J Med 2020.

297. Pranata R, Permana H, Huang I, Lim MA, Soetedjo NNM, Supriyadi R, Soeroto AY, Alkatiri AA, Firman D, Lukito AA: The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Diabetes Metab Syndr 2020, 14(5):983-990.

298. Thomas SA, Puskarich M, Pulia MS, Meltzer AC, Camargo CA, Courtney DM, Nordenholz KE, Kline JA, Kabrhel C: Association Between Baseline Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and Death Among Patients Tested for COVID-19. J Clin Pharmacol 2022, 62(6):777-782.

299. Wallace AW, Cirillo PM, Ryan JC, Krigbaum NY, Badathala A, Cohn BA: Association of the patterns of use of medications with mortality of COVID-19 infection: a hospital-based observational study. BMJ Open 2021, 11(12):e050051.

300. Wang Y, Chen B, Li Y, Zhang L, Wang Y, Yang S, Xiao X, Qin Q: The use of renin-angiotensin-aldosterone system (RAAS) inhibitors is associated with a lower risk of mortality in hypertensive COVID-19 patients: A systematic review and meta-analysis. J Med Virol 2020.

301. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L et al: Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res 2020.

302. Felber R, New W, Riskin SI: SARS-CoV-2 and the Angiotensin-Converting Enzyme 2 Receptor: Angiotensin-Converting Enzyme Inhibitor/Angiotensin 2 Receptor Blocker Utilization and a Shift Towards the Renin-Angiotensin-Aldosterone System Classical Pathway. Cureus 2024, 16(3):e55563.

303. Yin J, Wang C, Song X, Li X, Miao M: Effects of Renin-Angiotensin System Inhibitors on Mortality and Disease Severity of COVID-19 Patients: A Meta-analysis of Randomized Controlled Trials. Am J Hypertens 2022, 35(5):462-469.

304. Rysz S, Al-Saadi J, Sjostrom A, Farm M, Campoccia Jalde F, Platten M, Eriksson H, Klein M, Vargas-Paris R, Nyren S et al: COVID-19 pathophysiology may be driven by an imbalance in the renin-angiotensin-aldosterone system. Nat Commun 2021, 12(1):2417.

305. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW: Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. Hypertension 2004, 43(5):993-1002.

306. Burnier M: Telmisartan: a different angiotensin II receptor blocker protecting a different population? J Int Med Res 2009, 37(6):1662-1679.

307. Wienen Wea: A Review on Telmisartan: A Novel, Long-Acting Angiotensin II-Receptor Antagonist. Cardiovascular Drug Reviews 2000, 18(2):27.

308. Duarte M, Pelorosso F, Nicolosi LN, Victoria Salgado M, Vetulli H, Aquieri A, Azzato F, Castro M, Coyle J, Davolos I et al: Telmisartan for treatment of Covid-19 patients: An open multicenter randomized clinical trial. EClinicalMedicine 2021, 37:100962.

309. Roy-Vallejo E, Sanchez Purificacion A, Torres Pena JD,

Sanchez Moreno B, Arnalich F, Garcia Blanco MJ, Lopez Miranda J, Romero-Cabrera JL, Herrero Gil CR, Bascunana J et al: Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Withdrawal Is Associated with Higher Mortality in Hospitalized Patients with COVID-19. J Clin Med 2021, 10(12).

310. Alhaddad MJ, Almulaify MS, Alshabib AA, Alwesaibi AA, Alkhameys MA, Alsenan ZK, Alsheef HJ, Alsaghirat MA, Almomtan MS, Alshakhs MN: Relation Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19 Severity. Cureus 2022, 14(3):e22903.

311. ElAbd R, AlTarrah D, AlYouha S, Bastaki H, Almazeedi S, Al-Haddad M, Jamal M, AlSabah S: Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB) Are Protective Against ICU Admission and Mortality for Patients With COVID-19 Disease. Front Med (Lausanne) 2021, 8:600385.

312. Gnanenthiran SR, Borghi C, Burger D, Caramelli B, Charchar F, Chirinos JA, Cohen JB, Cremer A, Di Tanna GL, Duvignaud A et al: Renin-Angiotensin System Inhibitors in Patients With COVID-19: A Meta-Analysis of Randomized Controlled Trials Led by the International Society of Hypertension. J Am Heart Assoc 2022, 11(17):e026143.

313. Lee MMY, Kondo T, Campbell RT, Petrie MC, Sattar N, Solomon SD, Vaduganathan M, Jhund PS, McMurray JJV: Effects of renin-angiotensin system blockers on outcomes from COVID-19: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother 2024, 10(1):68-80.

314. Kow CS, Zaidi STR, Hasan SS: Cardiovascular Disease and Use of Renin-Angiotensin System Inhibitors in COVID-19. Am J Cardiovasc Drugs 2020.

315. Puskarich MA, Ingraham NE, Merck LH, Driver BE, Wacker DA, Black LP, Jones AE, Fletcher CV, South AM, Murray TA et al: Efficacy of Losartan in Hospitalized Patients With COVID-19-Induced Lung Injury: A Randomized Clinical Trial. JAMA Netw Open 2022, 5(3):e222735.

316. Tran KC, Asfar P, Cheng M, Demiselle J, Singer J, Lee T, Sweet D, Boyd J, Walley K, Haljan G et al: Effects of Losartan on Patients Hospitalized for Acute COVID-19: A Randomized Controlled Trial. Clin Infect Dis 2024, 79(3):615-625.

317. Jardine MJ, Kotwal SS, Bassi A, Hockham C, Jones M, Wilcox A, Pollock C, Burrell LM, McGree J, Rathore V et al: Angiotensin receptor blockers for the treatment of covid-19: pragmatic, adaptive, multicentre, phase 3, randomised controlled trial. BMJ 2022, 379:e072175.

318. Saavedra JM: Angiotensin receptor blockers and COVID-19. Pharmacol Res 2020, 156:104832.

319. Hariharan TS: COVID-19 Therapeutics Why Not Angiotensin Receptor Blockers (ARBs)? J Assoc Physicians India 2023, 71(11):71-75.

320. Mortensen EM, Nakashima B, Cornell J, Copeland LA, Pugh MJ, Anzueto A, Good C, Restrepo MI, Downs JR, Frei CR et al: Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. Clin Infect Dis 2012, 55(11):1466-1473.

321. Yano M, Matsumura T, Senokuchi T, Ishii N, Murata Y, Taketa K, Motoshima H, Taguchi T, Sonoda K, Kukidome D et al: Statins activate peroxisome proliferator-activated receptor gamma through extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase-dependent cyclooxygenase-2 expression in macrophages. Circ Res 2007, 100(10):1442-1451.

322. Schupp M, Janke J, Clasen R, Unger T, Kintscher U: Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation 2004, 109(17):2054-2057.

323. Mirjalili M, Soodejani MT, Raadabadi M, Dehghani A, Salemi F: Does Losartan reduce the severity of COVID-19 in hypertensive patients? BMC Cardiovasc Disord 2022, 22(1):116.

324. Talukdar J, Bhadra B, Dattaroy T, Nagle V, Dasgupta S: Potential of natural astaxanthin in alleviating the risk of cytokine storm in COVID-19. Biomed Pharmacother 2020, 132:110886.

325. Huang SH, Cao XJ, Liu W, Shi XY, Wei W: Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. J Pineal Res 2010, 48(2):109-116.

326. Xu MM, Kang JY, Wang QY, Zuo X, Tan YY, Wei YY, Zhang DW, Zhang L, Wu HM, Fei GH: Melatonin improves influenza virus infection-induced acute exacerbation of COPD by suppressing macrophage M1 polarization and apoptosis. Respir Res 2024, 25(1):186.

327.Silvestri M, Rossi GA: Melatonin: its possible role in the management of viral infections--a brief review. Ital J Pediatr 2013, 39:61.

328.Slominski AT, Kim TK, Slominski RM, Song Y, Qayyum S, Placha W, Janjetovic Z, Kleszczynski K, Atigadda V, Song Y et al: Melatonin and Its Metabolites Can Serve as Agonists on the Aryl Hydrocarbon Receptor and Peroxisome Proliferator-Activated Receptor Gamma. Int J Mol Sci 2023, 24(20).

329.Xia Y, Chen S, Zeng S, Zhao Y, Zhu C, Deng B, Zhu G, Yin Y, Wang W, Hardeland R et al: Melatonin in macrophage biology: Current understanding and future perspectives. J Pineal Res 2019, 66(2):e12547.

330.Huo C, Tang Y, Li X, Han D, Gu Q, Su R, Liu Y, Reiter RJ, Liu G, Hu Y et al: Melatonin alleviates lung injury in H1N1-infected mice by mast cell inactivation and cytokine storm suppression. PLoS Pathog 2023, 19(5):e1011406.

331.Ramlall V, Zucker J, Tatonetti N: Melatonin is significantly associated with survival of intubated COVID-19 patients. medRxiv 2020.

332.Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J et al: Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med 2021, 181(1):41-51.

333.Kewan T, Covut F, Al-Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B: Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study. EClinicalMedicine 2020, 24:100418.

334.Moreno-Perez O, Andres M, Leon-Ramirez JM, Sanchez-Paya J, Rodriguez JC, Sanchez R, Garcia-Sevila R, Boix V, Gil J, Merino E: Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: A retrospective cohort study. J Autoimmun 2020, 114:102523.

335.Tomasiewicz K, Piekarska A, Stempkowska-Rejek J, Serafinska S, Gawkowska A, Parczewski M, Niscigorska-Olsen J, Lapinski TW, Zarebska-Michaluk D, Kowalska JD et al: Tocilizumab for patients with severe COVID-19: a retrospective, multi-center study. Expert Rev Anti Infect Ther 2021, 19(1):93-100.

336.Aoyagi T, Sato Y, Baba H, Shiga T, Seike I, Niitsuma Sugaya I, Takei K, Iwasaki Y, Oshima K, Kanamori H et al: Case Report: Successful Treatment of Five Critically Ill Coronavirus Disease 2019 Patients Using Combination Therapy With Etoposide and Corticosteroids. Front Med (Lausanne) 2021, 8:718641.

337.Lovetrue B: The AI-discovered aetiology of COVID-19 and rationale of the irinotecan+ etoposide combination therapy for critically ill COVID-19 patients. Med Hypotheses 2020, 144:110180.

338.Bergsten E, Horne A, Arico M, Astigarraga I, Egeler RM, Filipovich AH, Ishii E, Janka G, Ladisch S, Lehmberg K et al: Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017, 130(25):2728-2738.

339.Hamizi K, Aouidane S, Belaaloui G: Etoposide-based therapy for severe forms of COVID-19. Med Hypotheses 2020, 142:109826.

340.Patel M, Dominguez E, Sacher D, Desai P, Chandar A, Bromberg M, Caricchio R, Criner GJ, Temple University C-RG: Etoposide as Salvage Therapy for Cytokine Storm Due to Coronavirus Disease 2019. Chest 2021, 159(1):e7-e11.

341.Takami A: Possible role of low-dose etoposide therapy for hemophagocytic lymphohistiocytosis by COVID-19. Int J Hematol 2020, 112(1):122-124.

342.Annweiler C, Beaudenon M, Gautier J, Gonsard J, Boucher S, Chapelet G, Darsonval A, Fougere B, Guerin O, Houvet M et al: High-dose versus standard-dose vitamin D supplementation in older adults with COVID-19 (COVIT-TRIAL): A multicenter, open-label, randomized controlled superiority trial. PLoS Med 2022, 19(5):e1003999.

343.Arachchillage DJ, Remmington C, Rosenberg A, Xu T, Passariello M, Hall D, Laffan M, Patel BV: Anticoagulation with argatroban in patients with acute antithrombin deficiency in severe COVID-19. Br J Haematol 2020, 190(5):e286-e288.

344.Piazza G, Campia U, Hurwitz S, Snyder JE, Rizzo SM, Pfeferman MB, Morrison RB, Leiva O, Fanikos J, Nauffal V et al: Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19. J Am Coll Cardiol 2020, 76(18):2060-2072.

345.Yonker LM, Kane AS, Swank Z, Papadakis L, Kenyon V, Han S, Lima R, Guthrie LB, Alvarez-Carcamo B, Lahoud-Rahme M et al: Viral spike antigen clearance

and augmented recovery in children with post-COVID multisystem inflammatory syndrome treated with larazotide. Sci Transl Med 2025, 17(809):eadu4284.

346. Zhang G, Nie S, Zhang Z, Zhang Z: Longitudinal Change of SARS-Cov2 Antibodies in Patients with COVID-19. J Infect Dis 2020.

347. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, Johnson M, Griffiths B, du Pre P, Mohammad Z et al: Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health 2020, 4(9):669-677.

348. Nagelkerke SQ, Dekkers G, Kustiawan I, van de Bovenkamp FS, Geissler J, Plomp R, Wuhrer M, Vidarsson G, Rispens T, van den Berg TK et al: Inhibition of FcgammaR-mediated phagocytosis by IVIg is independent of IgG-Fc sialylation and FcgammaRIIb in human macrophages. Blood 2014, 124(25):3709-3718.

349. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, Milner JD: Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. JAMA 2020, 324(3):294-296.

350. Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA, Jordan MB: Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. J Immunol 2014, 192(1):84-91.

351. Lerkvaleekul B, Vilaiyuk S: Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol 2018, 10:117-128.

352. Tremoulet AH, Pancoast P, Franco A, Bujold M, Shimizu C, Onouchi Y, Tamamoto A, Erdem G, Dodd D, Burns JC: Calcineurin inhibitor treatment of intravenous immunoglobulin-resistant Kawasaki disease. J Pediatr 2012, 161(3):506-512 e501.

353. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, O'Hara M, Suett J, Dahmash D, Bugaeva P et al: Characterising long COVID: a living systematic review. BMJ Glob Health 2021, 6(9).

354. Spudich S, Nath A: Nervous system consequences of COVID-19. Science 2022, 375(6578):267-269.

355. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, Winkler CW, Sun J, Dickey JM, Ylaya K et al: SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature 2022, 612(7941):758-763.

356. Matschke J, Lutgehetmann M, Hagel C, Sperhake JP, Schroder AS, Edler C, Mushumba H, Fitzek A, Allweiss L, Dandri M et al: Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 2020, 19(11):919-929.

357. Fernandez-Castaneda A, Lu P, Geraghty AC, Song E, Lee MH, Wood J, O'Dea MR, Dutton S, Shamardani K, Nwangwu K et al: Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell 2022, 185(14):2452-2468 e2416.

358. Klein J, Wood J, Jaycox JR, Dhodapkar RM, Lu P, Gehlhausen JR, Tabachnikova A, Greene K, Tabacof L, Malik AA et al: Distinguishing features of long COVID identified through immune profiling. Nature 2023, 623(7985):139-148.

359. Nazarinia D, Behzadifard M, Gholampour J, Karimi R, Gholampour M: Eotaxin-1 (CCL11) in neuroinflammatory disorders and possible role in COVID-19 neurologic complications. Acta Neurol Belg 2022, 122(4):865-869.

360. Altmann DM, Whettlock EM, Liu S, Arachchillage DJ, Boyton RJ: The immunology of long COVID. Nat Rev Immunol 2023, 23(10):618-634.

361. Finlay JB, Brann DH, Abi Hachem R, Jang DW, Oliva AD, Ko T, Gupta R, Wellford SA, Moseman EA, Jang SS et al: Persistent post-COVID-19 smell loss is associated with immune cell infiltration and altered gene expression in olfactory epithelium. Sci Transl Med 2022, 14(676):eadd0484.

362. Vermersch P, Granziera C, Mao-Draayer Y, Cutter G, Kalbus O, Staikov I, Dufek M, Saubadu S, Bejuit R, Truffinet P et al: Inhibition of CD40L with Frexalimab in Multiple Sclerosis. N Engl J Med 2024, 390(7):589-600.