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COVID-19-Associated acute respiratory distress syndrome (CARDS): Mechanistic insights on therapeutic intervention and emerging trends

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ABSTRACT

Aims: The novel Coronavirus disease 2019 (COVID-19) has caused great distress worldwide. Acute respiratory distress syndrome (ARDS) is well familiar but when it happens as part of COVID-19 it has discrete features which are unmanageable. Numerous pharmacological treatments have been evaluated in clinical trials to control the clinical effects of CARDS, but there is no assurance of their effectiveness.

Materials and Methods: A systematic review of the literature of the Medline, Scopus, Bentham, PubMed, and EMBASE (Elsevier) databases was examined to understand the novel therapeutic approaches used in COVID-19-Associated Acute Respiratory Distress Syndrome and their outcomes.

Key findings: Current therapeutic options may not be enough to manage COVID-19-associated ARDS complications in group of patients and therefore, the current review has discussed the pathophysiological mechanism of COVID-19-associated ARDS, potential pharmacological treatment and the emerging molecular drug targets.

Significance: The rationale of this review is to talk about the pathophysiology of CARDS, potential pharmacological treatment and the emerging molecular drug targets. Currently accessible treatment focuses on modulating immune responses, rendering antiviral effects, anti-thrombosis or anti-coagulant effects. It is expected that considerable number of studies conducting globally may help to discover effective therapies to decrease mortality and morbidity occurring due to CARDS. Attention should be also given on molecular drug targets that possibly will help to develop efficient cure for COVID-19-associated ARDS.

1. Introduction

The outburst of COVID-19 or SARS-CoV-2 has put terrible impact on global public health [1]. This novel disease was first erupted in December 2019, in China at Wuhan city and presently considered as a deadly disease. According to the current report, worldwide total COVID-19 cases are 179,260,990 with 3,882,169 deaths [2]. Severity in COVID-19 results from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections to viral pneumonia, therefore the manifestation is observed in combination namely viral pneumonia and ARDS. The disease has been said to be spread through zoonotic spill out of β-coronavirus type 2b which is nowadays spreading among humans [3,4]. Apart from inducing pneumonia and ARDS, corona virus family is likely to transform and contaminate susceptible populations, thereby causing a global threat [5]. The disease has a distinct pathophysiology and clinical pattern that confuses the efficiency of the presently accessible therapeutics.

1.1. Clinical symptoms and risk factors

A two-peak clinical course is involved in COVID-19 disease headed by an asymptomatic phase (also called as noiseless viral replication) [6,7]. During first phase, patient undergo with extensive viral replication of about five days after infection [8] and therefore the primary symptoms are generally coughing, fever and dyspnea [9]. Additional common symptoms comprises of headaches, anosmia, diarrhea, fatigue and some neurological symptoms [10]. Viral replication usually collapses about 5–7 days subsequent to the episode of symptoms [11]. After 7–10 days of appearance of symptoms, patients move into second phase and become seriously ill due to strong immune reaction and therefore the urgency to shift patient in ICU becomes high because of ARDS or multi-organ failure [12-14]. It has been revealed in 25 COVID-19 studies

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(involving 4881 severe and non-severe cases) [15] that the patients severely affected with COVID-19 were mostly suffering from diabetes and hypertension [15]. Apparently the pervasiveness of CARDS, acute kidney injury or shock was high in patients affected severely with COVID-19 giving rise to mortality rate of about 30%. [15]. Another analysis discovered that higher age, comorbidities involving obesity, diabetes, hypertension, COPD (chronic obstructive lung disease), renal disease, heart disease, immunodeficiency, male gender are risk factors for COVID-19 progression [16]. It has not been reported that COVID-19 may induce maternal or fetal complications in pregnant women. However pregnant women with co-morbidities affected with COVID-19 may have increased risks of complications. Therefore, they need to be monitored before and after delivery along with their infants [17]. Also cellular immunosuppression either due to acquired immunosuppression or any iatrogenic cause is responsible for disease progression and is observed mostly in severe cases [18,19].

1.2. Diagnostic criteria

The detection of SARS-CoV-2 infection can be assessed by specific PCR test which detects viral RNA in nasopharyngeal secretions [20-22]. COVID-19 affected patients is diagnosed with ARDS when it meets following diagnostic criteria: a) acute hypoxaemic respiratory failure b) worsening of respiratory symptoms within 1 week c) computed tomography (CT) which is not clearly visible due to lung collapse, nodules and effusions, [23,24]. ADRS builds up in 42% patients exhibiting COVID-19 associated pneumonia whereas 61–81% mostly requires serious care. COVID-19 associated ARDS has an expected time route which means ARDS develop at 8 or 9 days after beginning of symptom, as a result patients should be monitored properly during ARDS progression in COVID-19 [25]. Detection of SARS-CoV-2 by oropharyngeal swabs (OPS) and nasopharyngeal swabs (NPS) is an indispensable techniques for COVID-19 detection and its management. Difference in the sensitivity, detection rate and viral load in two sampling methods was evaluated in a prospective study in which 20 paired NPS and OPS specimens were collected from 120 confirmed COVID-19 patients. SARS-CoV-2 nucleic acid in swabs were detected by real-time RT-PCR. The results revealed that NPS displayed significantly higher SARS-CoV-2 detection rate, sensitivity, and viral load than OPS and NPS might decrease droplets production during swabs. Therefore NPS is suggested for diagnosing COVID-19 and monitoring SARS-CoV-2 load [25]. The two main parameters for monitoring patient's clinical condition and early detection of ARDS are respiratory rate and SpO2 [26]. Patient fitting into one of these following conditions are considered serious and immediately requires assessment "respiratory rate $\geq$ 30 breaths/min; SpO2 $\leq$ 92%; and PaO2/FiO2 $\leq$ 300 mmHg" [26]. Blood tests is also helpful in detecting disease severity as in Singapore it was found that COVID-19 ARDS patients requiring invasive mechanical ventilation had increased blood neutrophil counts and C-reactive protein levels (CRP) [27]. Therefore CRP may be regarded as earlier marker to predict early stage of COVID-19. It has been reported that Reverse transcriptase-polymerase chain reaction (RT-PCR) possesses 50–62% sensitivity towards COVID-19, but still displays substantial number of missed diagnosis. Chest CT score is an effective imaging tool for evaluating severity of pulmonary involvement in CARDS patients. CARDS patients display extensive abnormalities with higher degree of pulmonary condensation vs. ground-glass opacities [28]. Each of the five lung lobes are individually scored from 1 to 5 according to the distribution of affected parenchyma; (i) Representing less than 5% lobar involvement, (ii) 5–25% lobar involvement, (iii) 26–50% lobar involvement, (iv) 51–75% lobar involvement; (v) 5 > 75% lobar involvement. The final score will be the summation of individual lobar scores and will be out of 25 (total score); the total lung involvement is then obtained by multiplying the total score times 4. The chest CT density is also graded: 0 = normal attenuation, 1 = frosted glass density, 2 = ground-glass attenuation, 3 = consolidation. The lung parenchyma score is then multiplied by the square of the CT density score and points from all zones and added for a final total cumulative score that ranged from 0 to 900 [28].

2. Pathophysiology of COVID-19 induced ARDS

2.1. SARS-CoV-2 viral intrusion

The genome of SARS-CoV-2 is a single stranded RNA comprising of structural proteins spike (S), envelope (E), and membrane (M) that constitute the viral coat and the nucleocapsid (N) protein. These structural proteins are crucial for virus assembly and binding of virus–host cell. The S protein has two functional domains called S1 and S2. S1 holds an N-terminal domain and a receptor-binding domain (RBD) [29]. The receptor-binding motif (RBM) is localized within the carboxy-terminal half of the RBD and comprises residues that enable attachment of the S protein to a host cell receptor. The S2 subunit stimulates the fusion of viral and host membrane subsequent to cleavage of peptide bonds within the active site by cellular proteases known as TMPRSS2 or cathepsins. SARS-CoV enters into permissive host cells via interactions of SARS-CoV S protein RBD with the cell surface receptor angiotensin converting enzyme (ACE) 2 [26,29]. After viral penetration into respiratory cells, intracellular release of RNA takes place where the process of translation/replication gets started and then finally leading to virions exocytosis [30]. Virions exocytosis further causes spread of virus to the all the cells of organs. Virus interaction with ACE2 receptor also dysregulates RAAS function and increases vascular permeability, vasoconstriction and promotes inflammation [31]. ACE2 has anti-inflammatory and anti-fibrotic properties through its function of conversion of angiotensin (Ang -II) into Ang (1–7), but virus may reduce ACE2 expression and promote disruption of the immune system and contribute to the development of tissue fibrosis and such impact on ACE2 could be also involved in COVID-19 related fibrosis [32] (Fig. 2).Fig. 3

2.2. SARS-CoV-2-associated pneumonia and ARDS

SARS-CoV-2 infects airway epithelial cells or immune cells via binding to ACE2 receptors and stimulates release of Damage-associated molecular pattern (DAMP), along with production of inflammatory cytokines. The interaction between epithelial cells and immune cells leads to a broad range of clinical manifestations such as ARDS, pneumonia, cytokine storm and disseminated intravascular coagulation (DIC) [33] (Fig. 2). The entry of viral cell and its replication leads to widespread endothelial tissue damage that increases the permeability and accumulation of protein-rich fluids in alveolar and interstitial space [33]. During the exudative phase, several changes are observed such as fibrin deposition, hyaline membrane generation, large-scale tissue inflammation, necrosis and apoptosis that cause damage [33]. In addition to these, proliferation of fibroblasts, myofibroblasts, pulmonary vasculopathy may develop pneumonia and lung fibrosis with irreparable destruction may develop due to increased release of cytokines (such as Interleukin (IL)-1β and transforming-growth factor (TGF)- β) [34]. As result lung conformity in CARDS may be reduced or normal [34] whereas, patient self-inflicted lung injury (P-SILI) or potential ventilator-associated may have augmented pulmonary lesions over time [35] (Fig. 2).

2.3. Cellular immune responses

Although the inflammatory response in viral pneumonia is beneficial to help local tissues to fight with the infection, but the aggravated inflammatory responses in pneumonia patients may provoke the excessive proinflammatory cytokines release known as "cytokine storm", giving rise to harmful results such as fibrosis, disperse alveolar damage, progressive respiratory failure and multiple organ failure [36]. Cytokine storm is a hyperactive immune condition characterized by T cells proliferation, disturbance in M1/M2 balance. Macrophages consist of two

functional subtypes: M1 also known as pro-inflammatory macrophages engaged in developing pro-inflammatory reactions, chemotaxis, production of free radicals, and M2 is alternatively known as anti-inflammatory macrophages that reduces inflammation via producing growth factors (VEGF, EGF, PDGF) and suppressing effector T cells for repair [26,37]. Dysregulation in host immune response triggers hyper-inflammatory syndrome in COVID-19. The clinical feature of syndrome involves viral-induced hemophagocytic lymphohistiocytosis and macrophage activation with a cytokine storm [38] (Fig. 1). The cytokine storm usually occurs in viral respiratory infections such as H5N1 influenza, SARS-CoV-1, and SARS-CoV-2. Hyper inflammatory condition is confirmed in extremely pathogenic coronavirus-induced ARDS and also death and has brought major concern in developing therapies dealing with intense immune responses [39]. Overexpression of IL-6 is considered as a hallmark of cytokine storm as in many severe cases; IL-6 level was found extensively high than in mild cases. The pro-inflammatory cytokine production is facilitated by DAMPS released from infected cells and engagement of PAMPS with Toll-like-receptor (TLR 3, 7/8) [40]. COVID-19 patients admitted in ICU have shown elevated level of tumor-necrosis factors, IL-6 and monocyte chemotactic protein as compared to normal patients [40]. The neutrophil-to-lymphocyte ratio (NLR) is frequently detected high in COVID-19 patients that suggest severity of disease. Amongst several cytokines, one discrete intracellular signaling pathway is regulated by Janus kinases (JAKs) [41]. IL-6 has a major function in cytokine release syndrome (CRS) which triggers Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathway to perform various biological functions, involving, lymphocyte growth and differentiation, immune regulation and oxidative stress etc. [41]. Prominent IL-6 level in serum has been normally reported in seriously affected COVID-19 patients [42,43]. Therefore the restorative efficiency of IL-6 antagonists on COVID-19 patients is being evaluated by researchers. These result further approved JAK inhibitors as clinical management strategy for COVID-19. Antiviral response and chemoattractant pathways are regulated by type I interferon (IFN) in COVID-19 development [44]. Therefore, adequate type I IFN response is an essential aspect for fighting with viral infections and impairment in type I IFN responses is related to disease severity.

2.4. Endothelial dysfunction and thrombus formation

Endothelial dysfunction is responsible for COVID-19-associated vascular inflammation and coagulopathy [45]. In a small cohort study involving COVID-19 patients, the augmented levels of IFN-α and IFN-stimulated gene (ISG) were linked with viral load and disease severity. Viral invasion and type I interferon response characterizes the immunophenotypes during COVID-19 infection [46]. SARS-CoV-2 infection stimulates activation of IFN, complement system and generation of proinflammatory mediators that promotes endothelial cell damage [46]. As conferred that COVID-19 results in a hyper inflammatory response with extreme infiltration of inflammatory cells into the lung tissue and immune dysregulation, increasing the risk of vascular hyper-permeability, multiorgan failure and death [47]. Constant inflammation alters biological anticoagulant activities, decreases platelet reactivity and thrombus formation. Inflammatory cytokines such as TNF-α, IL-1 and IL-6, are the important mediators involved in coagulation start by inhibiting fibrinolysis activity and upregulating prothrombotic factors. Therefore inflammation and thrombosis are largely dependent on each other and their dysregulation may develop fetal results [48]. COVID-19 is linked with microvascular and macrovascular thrombotic disease as revealed through histology of pulmonary vascular with severe endothelial cell injury, microangiopathy, thrombosis and neoangenesis. A latest investigation examined that overall arterial and venous thromboembolism rate of ICU admitted COVID-19 patients was 31% and 5% [49]. The mortality rate amongst patients with thromboembolic events was 23% and without was 13% [49]. The accurate underlying mechanism of COVID-19-associated coagulopathy is still not completely understandable (Fig. 2).

3. Prevailing Pharmacotherapy for COVID-19-associated ARDS

3.1. Immunomodulators

3.1.1. Steroids

In either early or late phases of ARDS, steroids have been considered as a probable treatment as many studies have revealed that steroid induce beneficial effect by suppressing cytokine response while some studies have demonstrated its potential risks of suppressing of immune system and preventing viral elimination in Middle East Respiratory

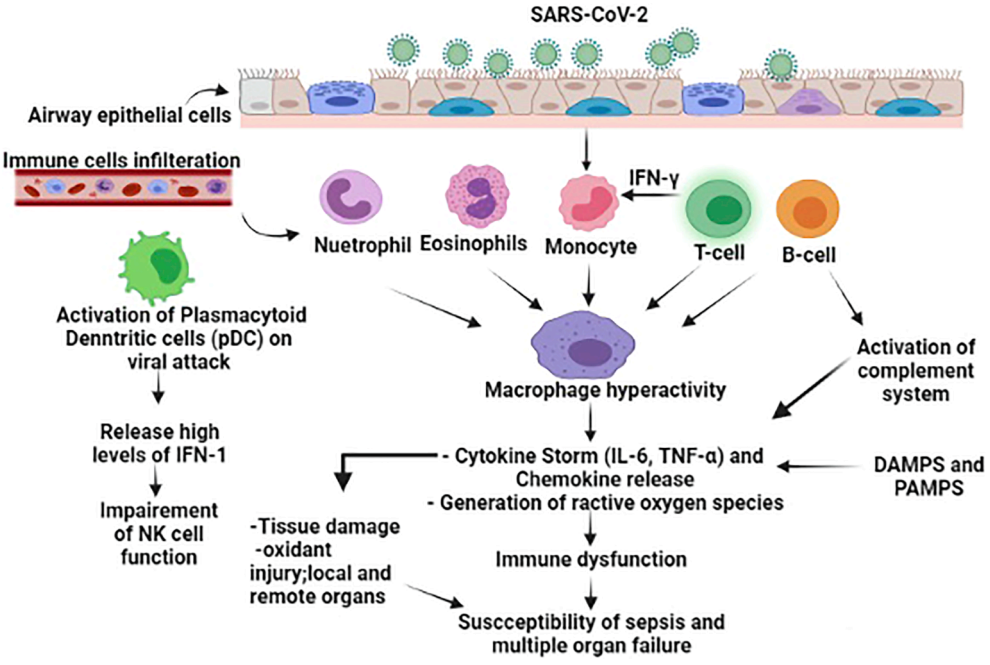

Fig. 1. Mechanisms of SARS-CoV-2 associated cytokine storm and associated damages. Infection with SARS-CoV 2 stimulates hyperinflammatory immune response on release of DAMPS and PAMPS which further stimulates cytokine (IL-6 and TNF-α) and chemokine release from immune cells, wherein epithelial-cell-mediated production of reactive oxygen species (ROS) damages tissue of local and remote organs and impairs immune function which may lead to multiple organ failure. Further release of IFN-1 by plasmacytoid dendritic cells (pDC) in response to viral attack also impairs NK cell function.

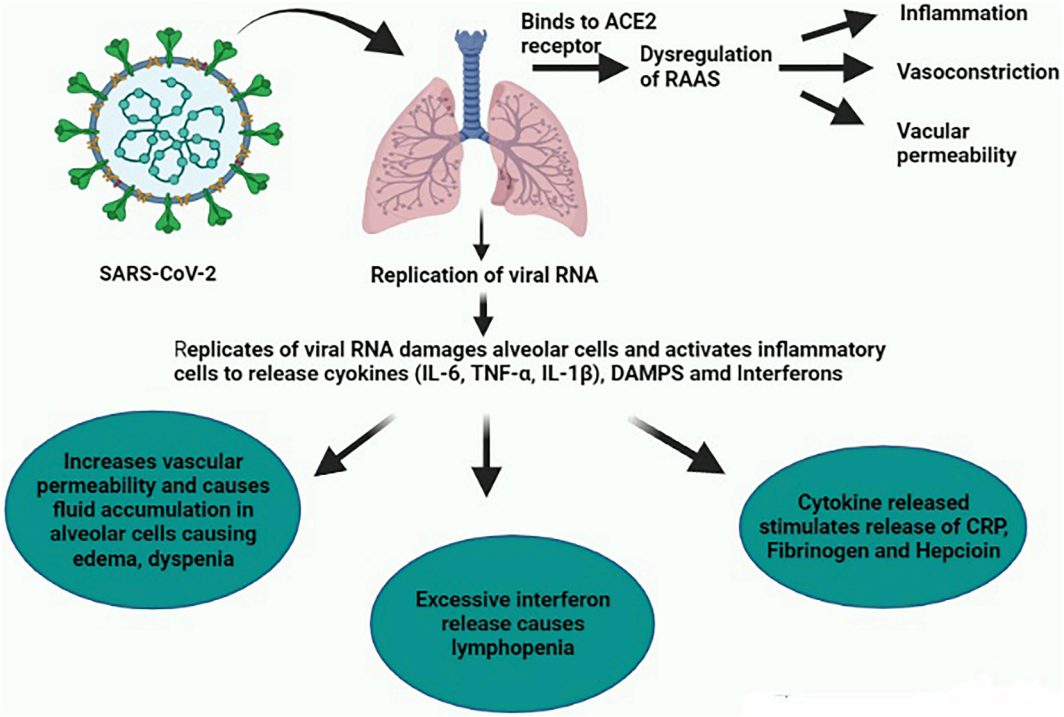

Fig. 2. Pathophysiology of COVID-19 induced ARDS.

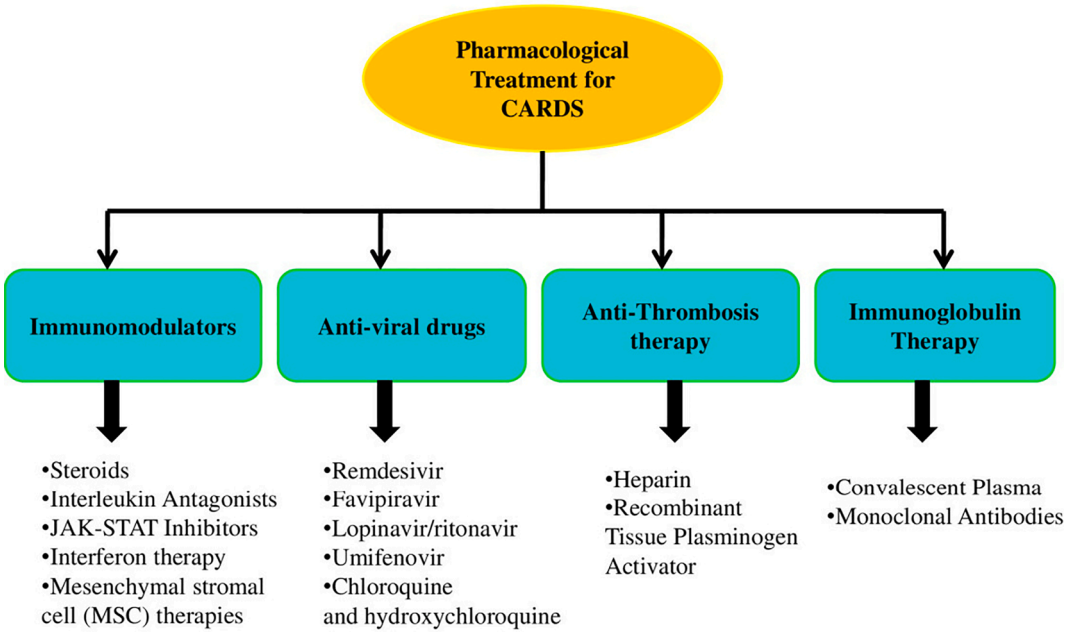

Fig. 3. Pharmacological Treatment Strategies for COVID-19associated ARDS.

Syndrome coronavirus (MERS) infection [50]. On the other hand, the beneficial effect of steroids in COVID-19 patients depends on dose, the extent of hyperinflammation, the incidence of ARDS and the phase of infection [51-53]. Recently, a study involving 46 COVID-19 patients demonstrated that administration of methylprednisolone at low dose improved the clinical effect as well as chest CT in the treated group [54]. One more huge retrospective study confirmed that treatment with methylprednisolone in COVID-19-associated ARDS patients decreased the possibility of death [55]. At present, various clinical trials at phase2/3 (ClinicalTrials.gov Identifier: NCT04343729) are assessing the efficiency and safety of methylprednisolone in CARDS patients. Expectedly, these studies will define the steroid's role in COVID-19 patients. Recently Dexamethasone has been reported to offer favorable effect against transience in COVID-19patients and therefore nowadays has attained a significant interest [56] (Fig. 2).

3.1.2. *Interleukin antagonists*

Thalidomide is an immunomodulatory drug that promotes T cell responses by inhibiting IL-6 and has shown valuable effects in preclinical viral or bacterial induced ARDS [57]. Currently thalidomide is in

Phase 2 (ClinicalTrials.gov Identifier: NCT04273581) clinical investigation against SARS-CoV-2. A recombinant IL-1 receptor antagonist known as Anakinra inhibited the physiological action of IL-1a and IL-1b by preventing their attachment with interleukin-1 type receptor in a competitive fashion and is usually employed in rheumatic diseases infection [58]. In a large phase 3 studies, Anakinra did not reduced death rate in patients with septic shock and sepsis, but enhanced survival in the subset of sepsis patients in a post hoc analysis with characteristics of Haemophagocytic lymphohisticytosis (HLH) (elevated levels of ferritin and liver enzymes) [59]. Currently, Anakinra is under clinical evaluation in 'COVID domain' of the REMAPCAP study (ClinicalTrials.gov Identifier: NCT02735707) (Fig. 2).

3.1.3. JAK-STAT inhibitors

JAK inhibitors are widely used in many inflammation driven diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel diseases [60]. There are numerous US FDA and European Medicine Association approved JAK inhibitors that are baricitinib, ruxolitinib, fedratinib, tofacitinib, upadacitinib, oclacitinib and some are under clinical investigation. Ruxolitinib was the first oral JAK1/2 inhibitor to be approved for neoplastic diseases [61]. Studies have demonstrated that JAK inhibitor has therapeutic implications in condition such as cytokine-driven inflammatory syndromes and sHLH (Haemophagocytic lymphohisticytosis) [62]. Therefore, the data supported the use of JAK inhibitor ruxolitinib in serious COVID-19 cases with dysregulated immune system [63]. Recently a study revealed the efficiency of ruxolitinib in severely affected COVID-19 patients, in which patients treated with ruxolitinib plus standard-of-care (SoC) showed rapid clinical recovery and effectiveness in contrast to control group [64]. Currently clinical trials are underway for investigating ruxolitinib in COVID-19 patients such as one of the trials (ClinicalTrials.gov Identifier: NCT04362137) is being sponsored by Novartis Pharmaceuticals to study the effect of ruxolitinib against COVID-19 associated cytokine storm. Recently Ruxolitinib was evaluated in a clinical study involving 18 COVID-19 patients with progressive acute respiratory distress syndrome [65]. Administration of ruxolitinib ameliorated the course of disease and avoided mechanical ventilation in 89% of treated patients [65]. On the other hand, the rate of COVID-19-associated ARDS patients shifted from NIV to mechanical ventilation with no ruxolitinib treatment was 57% and 27% of them had died [65].

3.1.4. Interferon therapy

Interferons emerge to have a multipurpose function in ARDS, amid inconsistent effects based on ARDS etiology and the type of interferon (type I, II or III) [66]. In a phase 2a study, Interferon-β1α (Type I interferon) showed promising results due to its anti-inflammatory, antifibrotic and anti-viral effects, but does not showed efficacy against ARDS in phase 3 study [67]. A recent study demonstrated that IFN-γ might facilitate entry of viral SARS-CoV-2 by upregulating ACE2 in the epithelial cells of lungs [68]. However interferon therapy could be a possible therapy for COVID-19. Type I interferons have displayed different inhibitory potencies towards SARS and MERS and have been evaluated in combination with antiviral drugs for these viral infections [68]. As revealed earlier, a recent phase 2 study of triple therapy comprising lopinavir/ritonavir, ribavirin, and IFN-β1β shown to enhance SARS-CoV-2 infected patient's recovery as compared to lopinavir/ritonavir only [69]. Other phase 2/3 clinical trials are evaluating the effectiveness of both type I and III interferons either in combination therapies or as a single agents in patients with SARS-CoV-2 [70] (Fig. 2).

3.1.5. Mesenchymal stromal cell (MSC) therapies

MSC possesses restorative and immunomodulatory effect and in ARDS preclinical models have shown effectiveness [71]. In a phase 1 trial, a bone marrow derived from human MSCs was infused in 9 patients affected with mild to severe ARDS [72]. However in phase 2a comprising 60 participants, MSC treatment did not improved patient's health but instead degraded their health [73]. A phase 1/2 study reported that MSC therapy reduced the demand of ventilator and ICU and also decreased the death rate [74]. Currently a study is recruiting for evaluating MSC derived from umbilical (ClinicalTrials.gov Identifier: NCT03042143), and remaining two are ongoing (ClinicalTrials.gov Identifier: NCT02444455, NCT03608592) [75]. Therefore MSCs has gained substantial attention as a treatment strategy for COVID-19 ARDS. In a recent clinical study involving 7 patients was infused with ACE2-/- MSCs at a single dose showed better pulmonary function and tolerance [76]. Numerous clinical studies are evaluating the effect of MSCs and MSC-derived exosomes in SARS-CoV-2 infected patients [77] (Fig. 2).

3.2. Anti-Viral drugs

3.2.1. Remdesivir

Remdesivir is a broad-spectrum anti-viral drug that has been formerly explored as an anti-Ebola drug [78]. Remdesivir interrupts viral replication via RNA polymerase and has shown to inhibit in vitro or in vivo SARS-CoV and MERS-CoV [79]. A recent study involving 61 infected patients with SARS-CoV-2 were treated with Remdesivir and were observed with 68% of improved cases in oxygenation and reduced the demand of mechanical ventilation in patients [80]. According to the recent unpublished report, Remdesivir condensed recovery time in COVID-19 patients but didn't show any effect on mortality rate and therefore in USA, the drug is being approved to be used in patients with COVID-19 [81]. Also in recent phase 3 study conducted in China involving 237 COVID-19 patients didn't demonstrated any considerable progress in clinical effect with Remdesivir treatment but displayed effect on recovery time [82]. Another recent placebo controlled study which involved 1000 patients treated with Remdesivir displayed that Remdesivir shortened recovery time and reduced lower respiratory tract infection [83]. More phase 2/3 clinical evaluations have been planned.

3.2.2. Favipiravir

Favipiravir is effective against other RNA viruses, poliovirus, rhinovirus, and respiratory syncytial virus and evaluated and developed as a broad spectrum anti-RNA virus drug, including lethal RNA virus infections (ClinicalTrials.gov Identifier: NCT04828564). Numerous other clinical trials are investigating the combined effect of Favipiravir with tocilizumab against influenza [84]. Favipiravir have been previously used for the treatment of Ebola and influenza. It has also revealed potential against COVID-19 [85]. Another combination (Favipiravir / ribavirin: Ribavirin is a guanosine analog that interferes with the replication of RNA and DNA viruses.

3.2.3. Lopinavir/ritonavir

Lopinavir/ritonavir is HIV protease inhibitors usually employed in combination therapies [86]. An open-labeled study involving 199 severely COVID-19 patients unluckily didn't display any clinical improvement; however mortality rate was less in treated group [87]. In a recently phase 2 study the combined effect of lopinavir/ritonavir with ribavirin and IFN-β1β was studied in mild–modest COVID-19 patients and revealed that the combination reduced viral shedding and hospital resides in comparison to lopinavir/ritonavir alone [88].

3.2.4. Umifenovir

Umifenovir is an anti-viral drug approved for use in influenza which alters viral contact with ACE2, and recently showed enhanced viral clearance in a retrospective study involving 50 COVID-19 patients as compared to lopinavir/ritonavir [89]. More studies are currently undergoing for investigating the safety and efficiency of Umifenovir in COVID-19 patients.

3.2.5. Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are antimalarial drugs that acts by preventing virus from fusing with the host cells via inhibiting

ACE2 receptor present on the membrane of host cells and reduces release of pro-inflammatory cytokine [90,91]. In preclinical models, Chloroquine has shown to inhibit lung injury caused by influenza A H5N1 virus [92] and SARS-CoV-2 infection in vitro [93]. It has been newly revealed that combination of hydroxychloroquine with azithromycin condensed viral load in 20 SARS-CoV-2 infected patients [94]. On the other hand, potential adverse effects such as cardiotoxicity have been informed with the use of combination of azithromycin with chloroquine and hydroxychloroquine in COVID-19 patients [95]. There are other clinical investigation in progress using Nitazoxanide (NTZ) either alone or in combination with other drugs (Ivermectin or Hydroxychloroquine) to treat COVID-19 patients (ClinicalTrials.gov Identifier: NCT04360356, NCT04361318). Nitazoxanide, an antiparasitosis has shown great potential for repurposing to treat a variety of viral infections including SARS-CoV and MERS-CoV by targeting both host and viral components [96] and is currently ongoing clinical trial to evaluate its efficacy in patients with COVID-19 (ClinicalTrials.gov Identifier: NCT04552483). Ivermectin is also an antiparasitic drug is widely used to treat worm infections and scabies. Numerous observational and randomized studies have evaluated Ivermectin for the treatment against COVID-19 infection and the results concluded that Ivermectin demonstrated a strong therapeutic efficacy against COVID-19 by reducing death rates [97] and currently it is undergoing clinical trial for in COVID-19 high risk patients (I-TECH), ClinicalTrials.gov Identifier: NCT04920942.

3.3. Anti-Thrombosis therapy

Thrombosis, both microvascular and macrovascular, is a well-known feature in multiple organs with fatal cases of COVID-19. Thrombosis may thus contribute to renal failure, hepatic injury and respiratory failure in COVID-19 patients [98]. Thrombotic stroke has been recently reported in young COVID-19 patients with no cardiovascular risk factors. The thrombotic events are responsible for increasing numbers of hospitalized patients infected with COVID-19 [98]. Anti-thrombotics for adults hospitalized with COVID-19 (ACTIV4) is currently being evaluated in phase IV (ClinicalTrials.gov Identifier: NCT04505774). The clinical outcome of COVID-19 patients treated with a quadruple therapy consisting of Zinc, Quercetin, Bromelain and Vitamin C treated in COVID-19 patients displayed anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activity as well as inhibited lipid peroxidation, platelet aggregation and stimulated mitochondrial biogenesis (ClinicalTrials.gov Identifier: NCT04468139).

3.3.1. Heparin

Dysfunctioning in coagulation process is one of the pathological complications in severe COVID-19 patients which results in pulmonary microvascular thrombosis and deep venous thrombosis [99]. Therefore anticoagulant therapy such as heparin has been suggested by some expert group as treatment regimens for these complications in severe COVID-19 patients, but its effectiveness have not yet proven. Heparin is currently undergoing in clinical “REMAP-CAP study (ClinicalTrials.gov Identifier: NCT02735707)”. Study such as “CHARTER study” on nebulized heparin is also undergoing] (Fig. 2).

3.3.2. Recombinant tissue Plasminogen Activator (rtPA)

Alteration in coagulation process and reduced fibrinolysis are the attributes of COVID-19 that leads to microvascular thrombosis of the lung vessels which are linked to ACP (Acute cor pulmonale) and ARDS [100]. Currently rtPA was evaluated in 67 year old patient affected with ACP with elevated levels of C-reactive protein, high ferritin values and dead alveolar space [100]. The effect was that rtPA reduced all these parameters, improved oxygenation and reduced ventilatory ratio. The rtPA effects may have been more significant if the patients wouldn’t have had certain comorbidities involving obesity and hypertension. In severely affected COVID-19-associated ARDS, micro-thrombosis is possibly observed as a unique phenotype characterized by high levels of D-dimers, an enlarged portion of dead space and hypercapnia. Recent clinical data have suggested that rtPA can be a potential therapy in COVID-19- associated ARDS [101]. Currently nebulized rtPA for ARDS due to COVID-19 is under phase 2 clinical evaluation (ClinicalTrials.gov Identifier NCT04356833).

3.4. Immunoglobulin therapy

3.4.1. Plasma therapy

One of the hopeful treatment strategies in COVID-19 patients is plasma therapy. It has been demonstrated that serum obtained from SARS-CoV-1 patients provided protection from SARS-CoV-2 infection. This strategy possibly will be more successful if prophylactically employed [102-104]. In critically ill H1N1 patients, convalescent plasma treatment decreased viral load and transience [105] and the similar effect was observed in seriously ill SARS-CoV-2 patients [106]. Treatment of convalescent plasma was well tolerated in a trial involving 5000 COVID-19 patients (ClinicalTrials.gov Identifier: NCT04338360) [107]. There are other trials ongoing (ClinicalTrials.gov Identifier: NCT04356534, NCT04372979) for the evaluation of effectiveness and safety of anti-SARS-CoV (Fig. 2).

3.4.2. Monoclonal antibody

The human monoclonal antibodies, Tocilizumab and sarilumab have shown therapeutic effects in patients suffering from Still’s disease intricated with SIRS and ARDS [108]. A new retrospective study involving 21 COVID-19patients suggested that treatment with tocilizumab improved lung oxygenation with improved CT lung opacity and decreased white cell counts [109]. Presently several phases 2/3 trials are evaluating sarilumab or tocilizumab for COVID-19 patients, with probable outcomes. The available pharmacotherapies have been summarized in the table below (Table 1).

4. Emerging molecular drug targets for COVID-19associated ARDS

4.1. NLRP3 inflammasome

The vigorous activation of innate immune system is a characteristic of COVID-19 severity that triggers intense release of proinflammatory cytokine and chemokines and IL-6 which is a special prognostic of COVID-19 death [110]. High extent of interleukins such as IL-1β and IL-6 were identified in autopsy tissues of SARS-CoV patients. The fatality causing due to inflammatory response has led to the development of immunoregulators to treat CARDS. Activation of immune system during viral infections is highly correlated with NLRP3 (Nod-like receptor family, pyrin domain-containing 3) inflammasome [111-113]. There are numerous literatures linking NLRP3 inflammasome and cytokine storm in the pathogenesis of COVID-19 patients [114]. The viral (SARS-CoV 3a) protein triggers the activation of NLP3 inflammasome in the lipopolysaccharide-primed macrophages and stimulates IL-1β secretion which leads to K^+ efflux and generation of mitochondrial reactive oxygen species [115]. NLRP3 comprises of inactive procaspase-1 and an adapter element apoptosis-associated speck-like protein containing a CARD (caspase activation and recruitment domain). Studies have reported that various internal and external stimuli or viral RNA activates NLRP3 inflammasome through pores formation and lysosomal degradation leading to pyroptosis and inflammation (associated cell death) [116]. NLP3 after activation converts an enzyme procaspase-1 into an active effector protease caspase-1 which then promotes maturation of pro-inflammatory cytokines for example IL-pro-IL-1β (pro-interleukin 1β) into its active form IL-1β [117]. These further stimulates other downstream inflammatory mediators such as interleukin 6 (IL-6), tumor necrosis factor (TNF), leukotrienes and prostaglandins. Consequently, the expression of IL-1β and other inflammatory mediators have been

Table1
Prevailing Pharmacotherapy for COVID-19-associated ARDS.

Type	Drug	Clinical Effect	Reference
Steroids	Methylprednisolone	"Reduced clinical effect such as hyperinflammation, chest infection and the incidence of ARDS. Currently various clinical trials at phase2/3 (NCT04343729) are investigating the effectiveness and safety of methylprednisolone in patients with CARDS"	[54]
	Dexamethasone	"Suppressed cytokine storm"	[56]
Interleukin Antagonists	Thalidomide (IL-6 antagonist)	"Promotes T cell responses by inhibiting IL-6 and has shown beneficial effects in preclinical viral or bacterial induced ARDS. Currently thalidomide is in Phase 2 (NCT04273581) clinical investigation against SARS-CoV-2"	[57]
	Anakinra	"Anakinra counteracts the biologic activity of IL-1a and IL-1b by competitively preventing their attachment with interleukin-1 type receptor. Currently, Anakinra is being trialled in the 'COVID domain' of the REMAPCAP study (NCT02735707)"	[58]
JAK-STAT Inhibitors	Ruxolitinib	"Reduced cytokine-driven inflammatory syndromes in severely affected COVID-19patients."	[64,65]
Interferon therapy	Interferon-β1α (Type I interferon)	"Showed promising effect in phase 2a study due to its anti-inflammatory, anti-fibrotic and anti-viral functions"	[67]
	IFN-β1β in combination with anti-viral drugs (lopinavir/ritonavir and ribavirin)	" Improved SARS-CoV-2 infected patient's recovery as compared to lopinavir/ritonavir only"	[69]
Stem cell therapy	Mesenchymal stromal cell (MSC) therapies	" A recent clinical study involving 7 patients were infused with single dose of ACE2-/- MSCs showed better pulmonary function and tolerance"	[76]
Anti-viral Drugs	Remdesivir	"Remdesivir interrupts viral replication via RNA polymerase and has shown to inhibit SARS-CoV and MERS-CoV. In COVID-19patients shortened recovery time and reduced lower respiratory tract infection"	[83]
	Favipiravir	"Favipiravir demonstrated considerable viral clearance and improved chest CT scans in COVID-19patients"	[85]
	Lopinavir/ritonavir	" Reduced mortality rate of COVID patients In a recent phase 2 study the combined effect of lopinavir/ritonavir with ribavirin and IFN-β1β was studied in mild–modest COVID-19patients which revealed that the combination reduced viral shedding and hospital stays compared to lopinavir/ritonavir alone "	[88]
	Umifenovir	"Showed enhanced viral clearance in a retrospective study of 50 COVID-19patients"	[89]
Anti-Thrombosis therapy	Heparin	"Heparin is currently undergoing in clinical REMAP-CAP study (NCT02735707)"	[98]
	Recombinant Tissue Plasminogen Activator (rtPA)	"Recent clinical data have suggested that rtPA can be a potential treatment for with COVID-19associated ARDS. Currently nebulized rtPA for ARDS due to COVID-19is being evaluate in phase 2 clinical study (NCT04356833)"	[100,101]
Immunoglobulin Therapy	Convalescent Plasma Therapy	"Convalescent plasma has shown to lessen viral load and mortality in critically ill SARS-CoV-2 patients. Further trials are ongoing for the evaluation of safety and effectiveness of anti-SARS-CoV-2-inactivated convalescent plasma in COVID-19patients (NCT04356534, NCT04372979)"	[106]
	Monoclonal Antibody (Tocilizumab and sarilumab)	"Monoclonal antibody blocks IL-6 receptor. A recent non-controlled retrospective study of 21 COVID-19patients suggested that tocilizumab	[109]

(*continued on next page*)

Table1 (*continued*)

Type	Drug	Clinical Effect	Reference
		treatment decreased white cell counts and improved CT lung opacity and lung oxygenation "	

observed in SARS-CoV infected epithelial cells, bronchial macrophages and pneumocytes or pulmonary tissues. The SARS-CoV contains one of the biggest viral RNA genomes of about 29.7 kb [118]. The genes codes for enzyme replicase responsible for the replication of new genomes that further encodes for structural protein "Spike (S), Envelope (E), Membrane (M) and Nucleoprotein (N)" there in all CoVs. With respect to SARS-CoV infection, E protein has shown to trigger pro-inflammatory cytokines which promotes lung inflammation, fluid buildup and damage of bronchoalveolar epithelial cells by initiating ion channel (IC) activities [119]. Studies have also demonstrated that mutant E protein deficient in IC showed better results with respect to low fluid buildup or edema in tissues. Beside these findings, it was observed that Hexamethylene amiloride (HMA), a HIV-1 virus Vpu channel inhibitor prevented coronavirus replication in cultured cells and also inhibited conductance of E protein ion channels both in human coronavirus 229E (HCoV-229E) and mouse hepatitis virus (MHV) [120]. Similarly ORF3, a protein and viroporin (a potassium (K^+) ion channel) is responsible for lysosomal dysfunction in host cell that further causes activation of caspase-1 either directly through efflux of potassium (K^+) ions resulting in NLRP3 inflammasome activation [121]. NLRP3 inflammasome activation further directs transcription of cytokine gene of pro-IL-1β and pyroptosis cell death mediated by NF-κB. Thus NLRP3 possesses strong inflammatory potential in SARS-CoVs infection and emerges out to be a considerable target whose inhibition may reduce COVID-19 induced lung tissue inflammation [122]. Efforts are being made to discover the potential role of NLRP3 inflammasome in various inflammatory diseases. Some naturally derived NLRP3 inflammasome inhibitor, Parthenolide (sesquiterpene lactone found in feverfew plant) in addition to synthetic compound Bay 11–7082 and related vinyl sulfone compounds have shown to exert inhibitory effect on NLRP3 inflammasome [123]. Noticeably, Bay 11–7082 and Parthenolide inhibited NLRP3 inflammasome and NF-κB inflammatory pathways and reduced lung inflammation and improved survival in SARS-CoV-infected animals. Pirfenidone also suppressed apoptosis and oxidative stress in a mouse model of LPS-induced acute lung Injury (ALI), where treatment with Pirfenidone decreased caspase activation and reduced inflammatory release of IL-1β and TGF-β [124]. Another recently available NLRP3 inflammasome inhibitor is Tetracycline that shown to reduce mortality, by reducing neutrophil infiltration, vascular leakage in murine LPS ALI model. It also reduced release of pro-inflammatory cytokine and caspase activation [125]. Currently, Pirfenidone is being investigated in clinical phase 3 (ClinicalTrials.gov Identifier: NCT04282902) for SARS-CoV-2 treatment.

4.2. Heme oxygenase-1 (HO-1)

Heme oxygenase, a ubiquitous enzyme has currently attained a lot of interest because of its multiple therapeutic effects in most disease conditions. There exist three isoforms of Heme oxygenase 1; HO-1, HO-2 and HO-3, HO-3 is the splice variant of HO-2 [126]. Out of these isoforms, HO-1 is also recognized as heat shock protein-32 encoded HMOX1 gene and its transcription is induced by various stimuli such as radiations, infections, toxins and injuries such as acute lung injury and lung I/R injury [127]. The physiological function of HO-1 is to promote heme oxidation to carbon monoxide (CO), ferrous iron and biliverdin (BV) [128]. BV then gets converted to bilirubin (BR) via enzyme biliverdin reductase. This mechanism makes BR more electrophilic and relatively increases BR affinity for Keap1-Nrf2 that stimulates induction of Nrf2-dependant antioxidant gene [129]. At present, no pre-clinical or clinical data is available to validate the beneficial role of modulating HO-1 in COVID-19, but administration of heme or induction of HO-1 could be beneficial in fighting SARS-CoV-2 infection by degrading these end-products [130].

4.2.1. HO-1 in inflammation

HO-1 performs an important role in cell survival as it provides protection against inflammation, oxidative stress and removes degraded proteins as revealed in vitro and in vivo models of acute lung injury and inflammation [131]. The upregulation of HO-1 in response to inflammation and oxidative stress has been discovered in numerous cells such as neutrophils, monocytes, basophils, vascular smooth muscle cells, endothelial cells and macrophages. In different lung disease models, HO-1 has displayed its anti-inflammatory action [132]. Higher expression of HO-1 was found in mononuclear cells of inflammatory lesions of carrageenan-induced lung inflammation model in contrast to peripheral mononuclear cells [133]. The enhanced HO-1 expression resulted in reduced inflammation, whereas pretreatment with HO-1 inhibitor stimulated inflammation and HO-1 inducer decreased inflammation. Further HO-1 also reduced HMGB1 release from macrophages and production of pro-inflammatory cytokine in LPS model via CO generation [134,135]. In another study, CO Supplementation and HO-1 induction in-vivo LPS induced septic shock model reduced HMGB, IL-β and TNF-α level in plasma. CO has also displayed anti-apoptotic and anti-inflammatory effects in vivo and in vitro models of lung ischemia/reperfusion via modulation of P38-MAPK pathway [136]. In another in-vivo model of LPS induced acute lung injury, treatment with BV reduced inflammation in bronchoalveolar epithelial cells and alveolus along with reduced pulmonary edema, by decreasing the expression of transcription factor NF-κB which is responsible for LPS-stimulated inflammation and cytokine production [137]. Recent facts discovered that HO-1 promoted BR increase in plasma levels and provided defense against endothelial dysfunction and inflammation. BR possesses anti-inflammatory and antioxidant effects via scavenging reactive oxygen species and nitric oxide. COVID-19associated ARDS patients are mostly under support of external ventilator that may lead to lung injury [138,139]. The unique features of ventilator-induced lung injury (VILI) are epithelial and endothelial damage pursued by release of various chemokines and cytokines along with leukocytes recruitment and extravasation [140]. There are numerous studies supporting the beneficial role of HO-1 in VILI by reducing mediators of inflammation (TNF-α, IL-10 and IL-8) and decreasing neutrophil. Though, HO-1 expression is beneficial but its overexpression may be harmful as it may promote excess CO release that may reduce anti-inflammatory response either by inducing prostaglandin endoperoxide synthase enzyme activation which further causes inflammatory cytokines production or by inhibition of stress induced inflammatory response from hypothalamus pituitary adrenal axis [131]. Likewise, high serum level of BR may cause toxicity such as bilirubin encephalopathy in central nervous system. Studies have demonstrated the effect of Curcumin, a HO-1 inducer. Long-term administration of curcumin for about 6 months dose 1 to 4 g/day had shown to increase cholesterol levels and the opposite effect was observed in short-term treatment. Therefore, while targeting HO-1 system, hormetic response should be measured first [141,142].

4.3. HO-1 in thrombosis

Various studies have confirmed the anti-thrombotic function of HO-1 in case of arterial or venous injury. In ferric chloride induced mice model, HO-1 induction inhibited microvascular or platelet thrombosis [143]. Fujita and co-workers demonstrated that CO inhibited progression of fibrin clots via inhibiting gene expression encoding PAI-1in mice model of ischemic lung injury deficient in HO-1. Furthermore, CO treatment and HO-1 gene induction displayed anti-thrombotic and anti-

inflammatory effects in an apoE-deficient hypercholesterolemic mice model of arterial thrombosis [144]. In another study, mice deficient in Hmox1 showed increased endothelial cell injury which leads to apoptosis and platelet-rich micro thrombosis formation as confirmed by increased plasma levels of TF and von Willebrand and exogenous administration of BV and CO reduced pro-thrombotic state and thrombotic events thereby demonstrating their role in arterial thrombosis formation. In a mouse model of sepsis, HO-1 inducer, hemin increased anticoagulant -activated protein C, Thromboplastin time as well as prothrombin time via HO-1 activation. Results from histopathological evaluation showed reduced quantity of thrombi and inflammation in lungs and liver [145]. Further HO-1 induction by transfection of HO-1 end products (CO and BV) reported to decrease clot size in venous thrombosis model of mice. In another study, treatment of CO-releasing agent in HO-1-deficient mice allogenic aortic transplant remarkably reduced arterial thrombosis and platelet aggregation [146]. It has been confirmed that HO-1 induction with the treatment of activated protein C in a mouse model of venous thrombosis reduced IL-6 production. Therefore all these studies propose that HO-1 induction via HO-1 inducer or heme degradation end-products (CO, BV, and BR) show anti-thrombotic effects by reducing endothelial injury, inflammatory responses and levels of pro-coagulant factors such as von Willebrand factor, tissue factor and PAI, thus HO-1 may be a proficient approach in preventing COVID-19 linked deaths as inflammation stimulated-coagulopathy is the most disturbing consequences of COVID-19 [147].

4.4. Proteinase-activated receptor 1 (PAR1)

One of the key mediators of platelet activation and aggregation is Proteinase-activated receptor 1 (PAR1), a G-Protein coupled receptor (GPCR) and also an instigator of the coagulation cascade. Activation of PAR1 is stimulated by a serine protease known as Thrombin or by PAR1 agonist via cleaving its amino terminal and revealing a ligand which further self stimulates the receptor [148]. The expression of PAR1 is found in all cell types related to the pathobiology COVID-19 involving pneumocytes, platelets, endothelial cells and fibroblasts. Thrombin produced from prothrombin is the part of coagulation process and the main constituent for coagulation process is the tissue factor. Production of tissue factor by macrophages, fibroblasts and endothelial cells in severe COVID-19 disease is induced by hyper inflammation [149]. Therefore elevated production of thrombin and tissue factor activates PAR1 in patients with severe acute lung injury or COVID-19-associated ARDS. PAR1 also regulates endothelial function besides its action on platelets [149,150]. Thrombin is protective at low concentration but at high concentration it promotes endothelial disruption or dysfunction. PAR1 displays pathological phenotype in epithelial and alveolar cells of the lung such as release of inflammatory factors and apoptosis. PAR1 is also responsible in promoting lung fibrosis by stimulating transformation of fibroblasts into myofibroblasts and increasing secretions of extracellular matrix proteins [151]. The pathophysiology of COVID-19 has put forward PAR1 as a potential target in COVID-19. Study on mouse model have suggested that PAR1 inhibition reduced inflammation and enhanced immune response to viral infection in host, whereas a study demonstrated PAR1 having protective role in viral infection [152]. The contradictory effects may be due to variation in viral load in animals undertaken in these studies. However the most of the studies (in vivo) keep up the idea that PAR1 plays pathological role in inflammation and infectious diseases and its inhibition may have beneficial effects against viral respiratory infections [153]. Therefore vorapaxar or atopaxar are PAR1 inhibitors that can be employed in trials, however their preclinical validation on COVID-19 models prior to clinical trials is needed as vorapaxar has major side effects such as fatal bleeding events, but atopaxar has fewer bleeding events as well as shorter half-life than vorapaxar [154]. Knowing these risks, carefulness is needed while evaluating the potential of PAR1 inhibition as a means of treatment in COVID-19 patients. Further preclinical studies should assess the outcomes of PAR1 antagonists on fibroblasts, alveolar epithelial cells and endothelial cells in animal models of COVID-19 [155,156]. Also the effect of PARP1antagonists in COVID-19 associated thrombosis need to be replicated in animal models. Efforts are being made for developing animal models for COVID-19 such as rhesus monkeys, ferrets and other organisms [156]. Studies on animal models may further help to describe the mechanism of protective effect of PAR1 inhibition. Currently, data regarding the effect of PAR1 on platelets and other cell types in mouse models of Acute respiratory distress syndrome (ARDS) and Acute lung injury (ALI) are available that can be further extended in COVID-19 relevant animal models.

4.5. The phosphoinositide 3 (PI3)-kinase/Akt pathway

Inhibition of Akt with therapeutic agents have been accounted to inhibit the expressions of angiotensin-converting enzyme 2 (ACE2) receptor which aids viral entrance into lung cells, therefore targeting Akt for COVID-19 seems to be feasible option as the use of angiotensin-converting enzyme (ACE) inhibitors aggravates COVID-19-associated ARDS [157-159]. In numerous disease states, PI3K/Akt pathway has shown to promote inflammation, whereas Akt1 gene deletion in mice following myocardial ischemia recovered cardiac function and reduced inflammation [160]. Also it has been revealed that Akt inhibition suppresses inflammation but inhibition of PTEN may promote inflammation via activation of Akt in regulatory T cells (Tregs) [161]. Adoptive relocation of Tregs also exhibited to restrain fibro proliferation and improved lung injury resolution in experimental animal model disclosing that rising Tregs number in ARDS lungs could be a novel approach to treat COVID-19 patients at complex points and it has been recently discovered that Tregs number can be increased in ARDS lung via Akt inhibition as demonstrated in mouse model of bacterial *endo*-toxin induced lung injury, promoting recovery and injury resolution [162]. ACE2 has a pathological role in lung inflammation and pulmonary arterial hypertension. Akt inhibitors for example MK2206 and triciribine are Akt have been accounted to improve the pathophysiological outcome of ACE2 in hepatic steatosis [163]. But, a connection needs to be established between ACE2 activation and Akt pathway in COVID-19 patients. Virus utilizes PI3-kinase/Akt pathway in host cell generally for its survival and replication and Akt inhibitors (triciribine and MK2206) either combination or alone could develop into a possible cure considerable for COVID-19 patients with ARDS [163]. On the basis of preclinical results from non-COVID-19 lung disease research, inhibition of Akt could raise Tregs in the lungs of COVID-19 patients which may ultimately suppress inflammation, fibro proliferation, vascular pruning and promoting injury resolution. However an extra preclinical experimental validation should be conducted in desired COVID-19 models (for example non-human primates) before clinical trials in COVID-19 patients.

4.6. P2X purinoceptor 7 (P2X7)

P2X7 receptors are the ligand-gated members of P2XR family which gets activated by elevated concentration of ATP during cell damage condition and releases into extracellular space. P2X7Rs expressions are mainly found in peripheral immune cells, macrophages of CNS and microglia [164]. P2X7Rs on activation allows entry of Na^{+}/Ca^{2+} and exit of K^{+}. The complications associated with acute respiratory distress syndrome (ARDS) such as pneumonia is the main reason of mortality and morbidity in Covid-19 patient and there is no efficient treatment until now [165]. In ARDS patients, high ATP levels were found in bronchoalveolar lavage fluid (BALF) and also in mice induced with LPS-induced acute lung injury (ALI) [166]. P2X7Rs are regarded as the main drivers of inflammation. The receptors on Macrophages/microglia contains patterns of recognition responsible for recognizing pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) or danger-associated molecular patterns (DAMPs), such as ATP

[167]. The activation of macrophages promotes cytokine release via two processes firstly by LPS mediated stimulation of toll-like receptor 4 and secondly ATP-induced P2X7Rs activation which further encourages NLRP3 induced caspase-1 activation and later IL-1β secretion [168]. As a result NLRP3 can be activated by SARS-CoV-2 viral proteins and P2X7 receptor. Activation of P2X7 receptor enhances chemokine and cytokine release such as IL-6, IL-8, TNF-α, CCL2, CCL3 and pro-fibrotic factors for example TGF-β. In P2X7 deficient mice model of silica-induced lung fibrosis or models of bleomycin, reduced inflammation was observed [169-171]. Thus, it suggests that P2X7 receptor deletion or antagonists might be of benefit for less severe COVID-19 patients. Cytotoxic NK cells and T lymphocytes are incapable to lyse virus-infected cells in Macrophage activated syndrome (MAS) and causes long term cytokine release common of this syndrome and of COVID-19 as well [172]. Besides, a key feature of ARDS is the wide pulmonary edema due to elevated level of VEGF and VEGF. The P2X7 receptor may induce in vivo VEGF release and neo-angiogenesis, thereby known as a potent inducer of VEGF release and blockade of P2X7 receptors inhibited VEGF-mediated increase in vascular permeability [173]. Thus, targeting P2X7 receptor may be beneficial to fight early phase in ARDS. Further, thromboembolic complications common amongst critically ill COVID-19 patients can be reduced by targeting P2X7 receptors as activation of these receptors leads to enormous release of tissue factor [174]. In mice model of ARDS, LPS was applied intratrachealy which induced lung inflammation similar to human ARDS [175]. LPS inhalation induces ALI, since LPS primarily targets plasma membrane pattern recognition receptors (PRRs), whereas SARS-CoV-2 targets intracellular receptors and P2X7 receptor blockade substantially condensed cytokine levels, infiltration of inflammatory cells and lung damage in ALI [176,177]. Deletion of P2X7 receptor also decreased alveolar macrophage and pro-IL-1α release in mice lungs treated with LPS [178]. The P2X7 receptor is recently proposed by developed radiopharmaceuticals as an inflammatory biomarker [176,179]. Low molecular compounds targeting P2X7 have gone through Phase I clinical trials and discovered their excellent safety profile [180] but due to their limited efficacy in various chronic inflammatory diseases investigated in Phase II trials lead most companies to stop clinical research on P2X7 receptors except Johnson & Johnson, who in 2019 started phase II clinical study to assess the efficacy of P2X7 receptor blockade in depression [181]. The therapeutic effects on blockade of P2X7 receptor has never been evaluated in uncontrolled hyperinflammation condition as in Covid-19. Therefore, P2XR might be a promising strategy and antagonists for P2X7 receptor could be beneficial in patient with COVID-19-associated ARDS with severe pneumonia.

4.7. Transmembrane protease serine 2 (TMPRSSS-2)

The interaction of viral protein also known as spike (S) protein with ACE-2 is catalyzed by a serine protease enzyme known as TMPRSSS-2 which further cleaves spike protein into S1 and S2 and then facilitates the interaction of these proteins with ACE2 receptor on host cell surface. S1 helps viral spike protein to bind with ACE-2, whereas S2 helps viral RNA to fuse in host cell membrane [182]. The expression of TMPRSSS-2 is highly found in nasal epithelial in goblet, ciliated cells of nasal epithelium and other parts of lung tissue [183]. Therefore blocking the activity of TMPRSS-2 might be a possible therapy for SARS-CoV-2. The general structure of this serine protease is illustrated by N-terminal domain and C-terminal catalytic domain [184]. The active site of the enzyme possesses extremely conserved nature of amino acid residues such as Ser441, His296, Gln438, Trp461 and Lys432 [184]. Studies have demonstrated that serine protease inhibitors can inhibit SARS-CoV-2 in the host cell. Camostat mesilate, a serine protease inhibitor reduced 65% mortality in mouse infected with SARS-Co. This clinically approved serine protease inhibitors is currently under clinical investigation (NCT04321096) for its effect against SARS-CoV-2 [185]. Therefore TMPRSS2 could be considered as a helpful tool for pharmacological research on SARS-CoV-2. There are other potential drug apart from camostat that can be repurposed to evaluate their in vitro activity against SARS-CoV-2, such as nafamostat and 4-(2-aminoethyl) benzenesulfonyl fluoride. In addition, mucolytic agents have been also proposed as TMPRSS2 inhibitor for COVID-19 therapy [186]. Further, a new therapeutic option is to use experimental and computational methods or estrogen and androgen-related compounds such as Enzatulamide, Genistein and Estradiol for transcriptional inhibition of TMPRSS2 [187]. TMPRSS2 expression can be altered by androgens and estrogens, therefore a study has suggested that inhibition of androgen pathways and activation of estrogen pathways may be a new strategy to manage symptoms in COVID-19 patients [188].

5. Future perspective and conclusion

At present, SARS-CoV-2 is causing rigorous illness all across the world sustaining transmission from human-to-human and has emerged as a serious danger to public health. Understanding of pathophysiological mechanism of COVID-19-associated ARDS (CARDS) has led to repurpose some approved drugs against SARS-CoV-2 infection such as Immunomodulators, anti-viral drugs, anti-thrombosis drugs and immunotherapy. Currently more pharmacological agents are undergoing clinical evaluation and their reports are underway. Apart from currently available pharmacological treatment for CARDS, attention should be also given on development of molecular drug targets and evaluation for their efficacy in preclinical and clinical platform that may help to manage the complications associated with CARDS. Despite of advanced scientific development, no permanent cure for diabetes, hypertension and cardiac disease exists. Also immune diseases such as HIV are also difficult to treat and therefore attention should be given on new strategies to maintain immune balance [189]. Zinc supplement in combination with anti-viral drug against viral infection is a dual-edged sword. Long-term Zinc treatment suppresses immune system. An in vitro study revealed that surplus Zinc supplementation can decrease IFN-γ expression in younger subject whereas in elderly persons increased interferon-alpha (IFN-α) production by leukocytes. However award-risk ratio is in favor of Zinc supplementation in COVID-19 [190,191]. There are less preclinical and clinical data on this aspect and results from currently ongoing trials employing Zinc in COVID-19 will throw light on the efficacy against viral infections in vivo. During viral infection, patients suffer from vitamin C deficiency due to high metabolic consumption which reduces the immunity of patient to fight COVID-19 associated detrimental effects so vitamin C supplementation is included in the treatment protocol of patients with viral infection. A recent study evaluated the role and effectiveness of vitamin C in counteracting the cytokines storm in cases with COVID-19 [192]. Vitamin D supplementation also have shown to provide protection to respiratory tract by killing enveloped viruses and preserving tight junctions. It also reduces cytokine storm by reducing pro-inflammatory cytokines production [193]. Combination of conventional treatment with micronutrients comprising Zinc and Vitamin C, D might improve the lung function in COVID-19 via maintaining immune balance and there are limited data available on clinical trials based on the associations of micronutrients and conventional treatment for COVID-19. However, some clinical studies are currently being accomplished to evaluate the effectiveness of certain nutrients in patients with COVID-19 (ClinicalTrials.gov Identifier: NCT04395768; NCT04264533 NCT03680274). The Clinical assessment of oral lactoferrin as a safe antiviral and immunoregulatory in treating COVID-19 disease (COVID-19_LF) is being carried out in phase 2 (ClinicalTrials.gov Identifier: NCT04412395). Currently Bevacizumab, an antiangiogenic drug is being evaluated in clinical phase 2 (ClinicalTrials.gov Identifier: NCT04954014) as a treatment for acute respiratory distress syndrome (ARDS) in COVID-19 patients. Therefore this review holds the information regarding viral pathophysiological mechanism, prevailing pharmacological treatment for COVID-19 patients and the emerging molecular drug targets that possibly will help to

develop effectual treatment for COVID-19-associated ARDS patients.

CRediT authorship contribution statement

Komal Thapa: Conceptualization. **Nitin Verma:** Visualization. **Thakur Gurjeet Singh:** Conceptualization, Supervision. **Amarjot Kaur Grewal:** . **Neha Kanojia:** . **Lata Rani:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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