Review Article

A narrative review of COVID-19-related acute respiratory distress syndrome (CARDS): "typical" or "atypical" ARDS?

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Background and Objective: The coronavirus disease of 2019 (COVID-19) is highly infectious and mainly involves the respiratory system, with some patients rapidly progress to acute respiratory distress syndrome (ARDS), which is the leading cause of death in COVID-19 patients. Hence, fully understanding the features of COVID-19-related ARDS (CARDS) and early management of this disease would improve the prognosis and reduce the mortality of severe COVID-19. With the development of recent studies which have focused on CARDS, whether CARDS is "typical" or "atypical" ARDS has become a hotly debated topic.

Methods: We searched for relevant literature from 1999 to 2021 published in PubMed by using the following keywords and their combinations: "COVID-19", "CARDS", "ARDS", "pathophysiological mechanism", "clinical manifestations", "prognosis", and "clinical trials". Then, we analyzed, compared and highlighted the differences between classic ARDS and CARDS from all of the aspects above.

Key Content and Findings: Classical ARDS commonly occurs within 1 week after a predisposing cause, yet the median time from symptoms onset to CARDS is longer than that of classical ARDS, manifesting within a period of 9.0–12.0 days. Although the lung mechanics exhibited in CARDS grossly match those of classical ARDS, there are some atypical manifestations of CARDS: the severity of hypoxemia seemed not to be proportional to injury of lung mechanics and an increase of thrombogenic processes. Meanwhile, some patients' symptoms do not correspond with the extent of the organic injury: a chest computed tomography (CT) will reveal the severe and diffuse lung injuries, yet the clinical presentations of patients can be mild.

Conclusions: Despite the differences between the CARDS and ARDS, in addition to the treatment of antivirals, clinicians should continue to follow the accepted evidence-based framework for managing all ARDS cases, including CARDS.

Keywords: Coronavirus disease of 2019 (COVID-19); acute respiratory distress syndrome (ARDS); COVID-19-related ARDS (CARDS); pathophysiological mechanism; prognosis

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Introduction

The coronavirus disease of 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global pandemic (1-3). Predominantly, COVID-19 patients experience mild clinical symptoms; however, 19% of those infected could experience severe or fatal symptoms, particularly COVID-19-related acute respiratory distress syndrome (CARDS) (4). It seems that CARDS is the main cause of death for COVID-19 patients. Hence, a research emphasis has been placed on the pathogenesis, clinical manifestations, and prognostic factors of CARDS. With the development of such studies, controversy has emerged surrounding whether CARDS is simply "typical" acute respiratory distress syndrome (ARDS), or is a particular subtype of ARDS with "atypical" pathophysiological and clinical features. It is increasingly inferred that CARDS might be different from other viral-driven related phenotypes. In a matched cohort study, Chiumello *et al.* demonstrated arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ratio was related to the proportion of non-aerated lung tissue in patients with "typical" ARDS, while there was no such correlation in CARDS patients. Furthermore, in CARDS, the severity of hypoxemia seemed not to be proportional to injury of lung mechanics, which was another point of distinction from classic ARDS (5). However, despite the above differences, there have been no study suggesting that the standard approaches used to manage classic ARDS should be modified for the management of CARDS. Rather, recent study has asserted that clinicians should continue to follow the accepted evidence-based framework for managing all ARDS cases, including CARDS (6). However, management approaches for CARDS are continually evolving with the accumulation of clinical experience (7). In this study, we capture the current understanding of CARDS, including pathophysiological mechanism, manifestations, diagnosis and differential diagnosis, treatment, as well as management and prognosis biomarkers. We further highlight and elucidate the differences between typical ARDS and atypical CARDS from the above aspects. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3717/rc).

Methods

The present study was conducted through the digital libraries of West China Hospital, Sichuan University, Jiangsu, China. We collected the associated literature about the pathophysiological mechanism, clinical manifestations, diagnosis, treatment, as well as the management and prognosis biomarkers of CARDS. All the data were collected from National Center for Biotechnology Information (NCBI) database, PubMed. For data collection, we used some Medical Subject Headings (MeSH) terms and their combinations in title/abstract: "COVID-19", "CARDS", "ARDS", "pathophysiological mechanism", "clinical manifestations", "prognosis biomarkers", and "clinical trials". *Table 1* describes the study sequence and details.

Mechanism of CARDS

Although the lung mechanics exhibited in CARDS grossly match those of classical ARDS (8), there are some atypical manifestations of CARDS (*Figure 1*): the separation between the maintenance of relatively good respiratory mechanics and the severity of the hypoxemia and an increase of thrombogenic processes (9-11). Based on different pathophysiology, patients with CARDS are divided into two phenotypes: L phenotype, with almost normal lung compliance, and H phenotype, with reduced lung compliance (12).

The hypoxemia caused by the L phenotype is likely attributed to a pulmonary vascular dysregulation leading to a mismatched ratio of ventilation to perfusion rather than an inherent problem of the pulmonary alveoli (10,13). This is probably related to the binding properties of SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2) receptors of endothelial cells and arterial smooth muscle cells. Type L patients are responsive to the increase of FiO_2 to reverse hypoxemia.

To the contrary, the H phenotype is attributed to hyper-inflammation that causes direct damage to the lungs and eventually leads to ARDS. The process of pathophysiology is as follows: the first 7–10 days (exudative stage) show interstitial/alveolar lymphocytic infiltration in the lung, scarcity of neutrophils (14), multinucleated syncytial cells, diffuse alveolar damage (DAD) with necrosis of endothelial and types I/II epithelial cells, and widespread microthrombosis with microangiopathy (15,16). These changes eventually lead to pulmonary edema, hyaline membrane formation, decreased pulmonary compliance, and difficulties in pulmonary ventilation and gas exchange. Type H patients should be treated as severe ARDS cases,

Table 1 The search strategy summary

Items	Specification
Date of search	2022-01-04 to 2022-05-30
Databases and other sources searched	NCBI PubMed
Search terms used (including MeSH and free text search terms)	“COVID-19”, “CARDS”, "ARDS", “pathophysiological mechanism”, “clinical manifestations”, “prognosis biomarkers”, and “clinical trials”
Timeframe	1999 to 2021
Inclusion and exclusion criteria	The study collected the relevant literature published in English from 1999 to 2021. The literatures of COVID-19 and ARDS was mainly covered
Selection process	Dan Pu, Xiaoqian Zhai and Yuwen Zhou jointly collected and assembled the data. Then Yao Xie, Liansha Tang and Liyuan Yina conducted the classification and analysis of the information. Finally, all authors reached an agreement on the manuscript
Any additional considerations	None

MeSH, Medical Subject Headings; NCBI, National Center for Biotechnology Information; COVID-19, coronavirus disease of 2019; CARDS, COVID-19-associated acute respiratory distress syndrome; ARDS, acute respiratory distress syndrome.

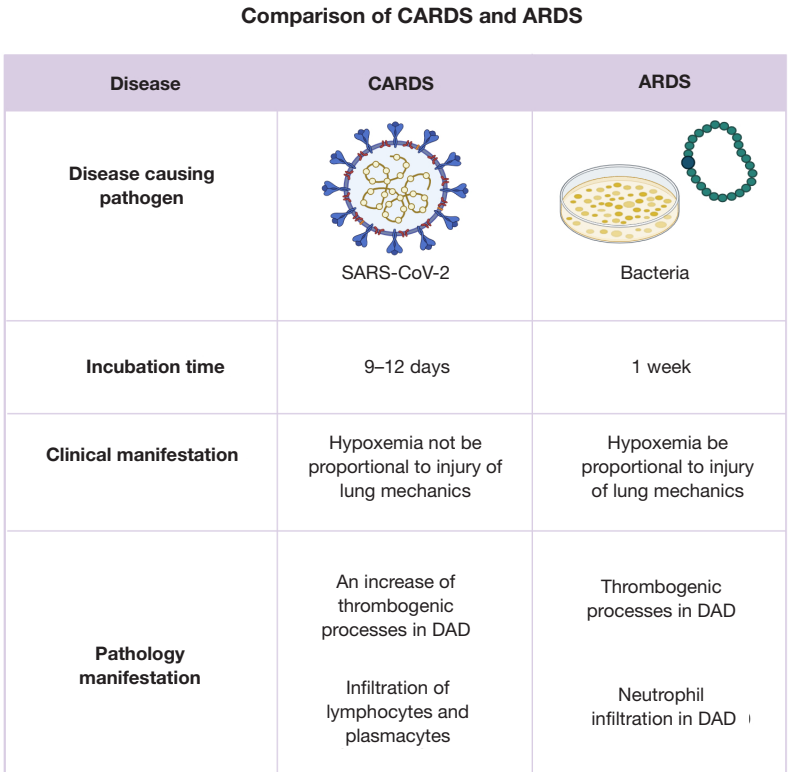

Figure 1 Comparison of CARDS and ARDS. Created with BioRender.com. CARDS, COVID-19-related acute respiratory distress syndrome; ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; DAD, diffuse alveolar damage.

including higher positive end-expiratory pressure (PEEP), if compatible with hemodynamics, prone positioning, and extracorporeal support.

Clinical manifestation

Based on clinical data available, the incidence of CARDS ranges from 14% to 67% (17-21). Classical ARDS commonly occurs within 1 week after a predisposing cause, yet researchers have reported that the median time from symptoms onset to CARDS is longer than that of classical ARDS, manifesting within a period of 9.0–12.0 days (1,17,22-24) (*Figure 1*). Similar to the classical ARDS, the clinical manifestations of CARDS usually include fever, dry cough, cyanosis of the mouth and lips, and respiratory distress which cannot be adjusted by normal oxygen therapy (25,26). A distinguishing feature of COVID-19 disease is that a lack of dyspnea is recognized in the most critical cases (26), the major reason for which is the direct neurotoxic impact of the virus and a general response caused within the infectious context (27). There are two mechanisms associated with it: one is the direct invasion of SARS-CoV-2 into ACE2-expressing brain cells in the limbic system (especially in the insula), and the second is the indirect toxic effect on the cortical network, which plays a major role in expressing the sensation of dyspnea, through cytokine storm (28). Apart from typical clinical manifestations, CARDS presents some atypical symptoms: it always manifests severe hypoxemia with well-preserved lung mechanics, although in classical ARDS, severe hypoxemia is always associated with poor lung compliance (29,30). Meanwhile, some patients' symptoms do not correspond with the extent of the organic injury: a chest computed tomography (CT) will reveal the severe and diffuse lung injuries, yet the clinical presentations of patients can be mild (29). Similarly, the results of laboratory tests, including indexes of hemodynamics and tissue perfusion, may be relatively stable in some patients with CARDS (21).

Diagnosis

Clinical diagnosis of CARDS is the same as that of classical ARDS, which is based on the Berlin criteria on the prerequisite of molecular diagnosis of COVID-19 (31). Usually, ARDS is divided into mild [200 mmHg < PaO_2/FiO_2 ≤300 mmHg with PEEP or continuous positive airway pressure (CPAP) ≥5 cmH_2O], moderate (100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cmH_2O), and severe (PaO_2/FiO_2 ≤100 mmHg with PEEP ≥5 cmH_2O) (24). However, some researchers have indicated that the Berlin definition is not fully suitable for the diagnosis and grading of CARDS because of its poor specificity to the diagnosis of DAD—the common histopathologic hallmark of ARDS which is more frequent in CARDS (32,33). The incidence of identification of DAD increases from less than 50% to 69% when Berlin-based diagnosis of classic ARDS is made after 3 days from the symptom onset. However, the median time of occurrence for CARDS is 9 days (34).

Hematologic tests

Abnormalities of hematologic indexes of CARDS present similarly to those of classical ARDS. Lymphopenia, neutrophilia, and thrombocytopenia are observed in blood routine and the deviation from the normal values always indicates the severity (18,35,36). Inflammatory responses lead to the overexpression of infection-related biomarkers including interleukin-6 (IL-6), interleukin-8 (IL-8), vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), granulocyte colony-stimulating factor (GCSF), tumor necrosis factor-α (TNF-α), complement 3 (C3), macrophage inflammatory protein 1-alpha (MIP1A), interferon (IFN)-inducible protein-10 (IP10), C-reactive protein (CRP), serum amyloid A, ferritin, and hepcidin. Among these, median IL-6 levels in hyper-inflammatory ARDS have been shown to be 10- to 200-fold higher than those in CARDS patients (37). Of note, higher concentration of these biomarkers is usually related to more severe disease (1,38-41).

Pathology manifestation

In both ARDS and CARDS, DAD is the major pathological manifestation, and was detectable in all lobes with a prominent distribution in middle and lower lobes (42). Differing from neutrophil infiltration in DAD of ARDS, patients who have died from CARDS have exhibited infiltration of lymphocytes and plasmacytes and a lack of neutrophils in both lungs (12,42) (*Figure 1*). Meanwhile, patients with DAD in CARDS developed more thrombotic complications compared to those with classical ARDS (43,44) (*Figure 1*). In addition to different features in DAD, CARDS presents other atypical pathological features. Enlarged pneumocytes and multinucleated syncytial cells have been observed, indicating viral-induced cytopathic-

like changes in the absence of intranuclear or intracytoplasmic viral inclusions (42).

The recommended treatment of CARDS

Although early studies have shown that CARDS has a unique function that distinguishes it from the historical ARDS, emerging evidence suggests that the respiratory mechanisms of ARDS patients are roughly similar, regardless of SARS-Cov2 infection. However, in terms of treatment, it should not be ignored that CARDS and ARDS involve some different pathophysiological aspects. In ARDS patients, due to the hyper-inflammation, the stability of the alveoli is always reduced, accompanied by pulmonary edema, pulmonary blood flow damage, and pulmonary blood vessel obstruction, resulting in hypoxemia. However, in CARDS, lung compliance remains almost normal, along with increased lung microvascular and macrovascular thrombosis when COVID-19 is severe. From this perspective, the breathing strategy is determined based on the homogeneity and heterogeneity in ARDS and CARDS.

Prevention of venous thromboembolism

A prospective cohort study (44) showed that the incidence of thrombotic complications in COVID-19 intensive care unit (ICU) patients is very high. Some 42.6% of CARDS patients were diagnosed with clinically relevant thrombotic complications during their stay in the ICU, especially, pulmonary embolism (16.7%) (45). Therefore, it is recommended that all COVID-19 patients admitted to the ICU should be strictly administered thromboprophylaxis where there are no contraindications, even in the absence of substantiating evidence (46). To date, several guidelines have recommended low molecular weight heparin for treatment severe COVID-19 patients with hypercoagulation.

Streptokinase, one of the thrombolytics, was recently found to promote lung function and oxygenation, and decrease ICU stay length and mortality in a randomized controlled trial (RCT) recruiting 60 ARDS patients without response to standard therapy (47). Besides, the results of previous phase I clinical trial reported that tissue plasminogen activator (tPA) used as salvage therapy for ARDS yielded significant improvements in PaO_2/FiO_2 (48). Preliminary studies have reported that tPA may improve recovery of ARDS patients and reduce COVID-19-related mortality (49,50). Anti-thrombosis therapy, as a potential therapy, is being evaluated in a few studies of CARDS patients on the basis of the pulmonary microthrombosis reports.

Respiratory support

Respiratory support plays an important role in the management of patients with CARDS and ARDS. Although the risk factors of CARDS associated with respiratory failure that require mechanical ventilation are not clearly described in the limited literature available, the risk factors associated with severe disease include older age (>60 years), male gender, and complications such as diabetes, chronic respiratory diseases, cardiovascular diseases, malignant tumors, and immunodeficiency (51). In addition, early in the pandemic of COVID-19, research demonstrated the differences between CARDS and classical ARDS and suggested different ventilatory management in CARDS. However, according to the gradually enriched understanding of CARDS, it is reasonable to employ a similar strategy at this stage, despite residual gray areas in the understanding of COVID-19 (52,53).

Respiratory support of mild ARDS

Patients with PaO_2/FiO_2 <300 mmHg should be administrated oxygen treatment immediately. A high-flow nasal cannula (HFNC) or a mask for oxygen supplementation could be implemented at the initial stage and the respiratory distress and/or hypoxemia should be promptly re-evaluated in time in the case of delayed intubation. In the absence of indications for tracheal intubation, patients with CARDS who cannot obtain a HFNC should undergo a close monitoring test of nasal intermittent positive pressure ventilation (NIPPV). For patients with persistent hypoxemia who have not undergone tracheal intubation despite increased supplemental oxygen demand, an awake prone position should be considered to improve oxygenation (CIIa), as reports have indicated that awake prone positioning could improve the overall median oxygen saturation of these patients (30). Nonetheless, considering the risk of viral transmission to other patients and health care workers, HFNC are not implemented in emergency rooms, unless negative pressure single rooms are available. A study has confirmed that HFNC could improve the outcome of patients with acute hypoxemic respiratory failure when the optimal oxygen saturation (SpO_2) ranged from 92% to 96% (54).

Respiratory support of moderate-severe ARDS

For adult patients with moderate-to-severe ARDS, it is recommended to ventilate in the prone position for 12–16 hours a day (BIIa). This ventilation strategy can evenly distribute the gas-tissue ratio and lung stress and strain distribution, yielding a significant improvement in arterial blood gas (55). Some clinical trials have convincingly shown that ARDS patients with PaO_2/FiO_2 <150 mmHg can reduce mortality by ventilating prone for at least 16 hours a day (56,57). To date, no study has described the clinical course of prone position ventilation in patients with COVID-19. However, we infer that these patients should also benefit from prone ventilation.

Patients with CARDS that have indications as follows for invasive mechanical ventilation should receive endotracheal intubation: (I) respiratory distress aggravation: when hypoxemia cannot be improved (SPO_2 ≤93%), the frequency of breathing ≥35 times/minute, or the tidal volume (Vt) is too large (>9 to 10 mL/kg weight) under HFNC or NIPPV treatment. (II) Tissue hypoxia or lactic acid elevation: the performances of tissue hypoxia aggravate, such as increasing lactic acid or decreasing central venous oxygen saturation ($ScvO_2$). (III) Hemodynamic instability or consciousness disorder. However, invasive mechanical ventilation has two sides. On the one hand, it potentially saves lives. On the other hand, it also causes ventilator-induced lung injury (VILI), exacerbating lung damage in ARDS patients and eventually leading to multiple organ failure. Reducing VILI may be achieved through low Vt ventilation (4–8 mL/kg), plateau pressures <30 cmH_2O, a conservative fluid strategy, higher PEEP. The recommendation comes from the experience of non-CARDS experience whereby higher PEEP in patients with moderate (PaO_2/FiO_2 100–200 mmHg) and severe ARDS (PaO_2/FiO_2 <100 mmHg) leads to lower rates of ICU mortality (58).

Furthermore, in ARDS patients, the analgesia and sedation effects should be adjusted according to the specific needs of the patient to avoid lung injury during the ventilation. Early neuromuscular blocking has been suggested to reduce 90-day mortality (59), although evidence remains controversial (60). Therefore, it is suggested that neuromuscular blocking agents (NMBA) should be used in patients with persistent ventilator dyssynchrony, and patients needing ongoing deep sedation prone ventilation, or persistently high plateau pressures (61).

An extracorporeal membrane oxygenator (ECMO) should be taken into consideration if a patient present with persistent hypoxemia, regardless of whether lung protective ventilation measures have been taken or not. The venovenous ECMO (vv-ECMO) has traditionally been used to provide adequate tissue oxygenation, to support patients with severe ARDS. However, the efficacy of ECMO in patients with ARDS remains controversial. A study showed that the use of ECMO in severe ARDS patients does not significantly reduce the 60-day mortality compared with conventional mechanical ventilation strategies including ECMO as a rescue therapy (62). There has been one study that demonstrated that the use of vv-ECMO in adults with severe ARDS can reduce 60-day mortality when compared with conventional mechanical ventilation, despite a moderate risk of major bleeding (63). Recently, guidelines have recommended that ECMO is used in the treatment of severe ARDS patients (64). However, in CARDS patients, the role of vv-ECMO is uncertain. One study demonstrated that the mortality rate was similar between ARDS and CARDS patients with vv-ECMO, which indicated that the use of vv-ECMO can achieve a similar effect in CARDS and ARDS patients (65). Patients with severe COVID-19 receiving ECMO support should be monitored closely for multiple drug-resistant bacteria (*Klebsiella pneumoniae*, *Baumann bacillus*, *Pseudomonas aeruginosa*, etc.) infections which will lead to poor prognosis. Due to the uncertain benefits and possible risks, the National Institutes of Health (NIH) guideline neither recommend nor advise against the use of ECMO in patients with COVID-19 and refractory hypoxemia.

Pharmacological therapy of CARDS

The pharmacologic therapy of CARDS does not appear "atypical". Most therapies of CARDS take the therapies of "typical" ARDS caused by other factors for reference, due to the similar critical physiopathologic processes such as cytokine storm. Actually, the pivotal point of combating CARDS may be anti-COVID-19 therapy itself. Here, we have summarized the following pharmacologic therapies of CARDS.

Antivirals

Remdesivir (GS-5734), as a broad-spectrum antiviral drug,

was regarded the most promising drug for treating severe COVID-19, but disappointing results have emerged. Study published in the Lancet reported no observable effect of remdesivir on the recovery or mortality of hospitalized patients with COVID-19 compared to placebo controls (66). Thus, Remdesivir was fails to be used to treat severe COVID-19.

Anti-inflammatory and immunoregulatory therapy

Corticosteroids

Owing to the anti-inflammatory and immune-modulating properties, corticosteroids have been widely applied for CARDS. However, the application of corticosteroids on CARDS patients remains controversial. The World Health Organization (WHO) (67) conducted a prospective meta-analysis, which pooled data from seven trials (RECOVERY, CoDEX, REMAP-CAP, CAPE COVID, and another 3 trials), to evaluate the response of corticosteroids to critically ill COVID-19 patients. Among these trials, over 50% of patients came from the RECOVERY trial. The RECOVERY trial confirmed for the first time that low-dose dexamethasone (6 mg/d, no more than 10 days) can reduce less than 28-day mortality among patients receiving invasive mechanical ventilation or oxygen alone (68). Based on that, medical officers in some countries have recommended to use glucocorticoids in patients with serious COVID-19 (69). In the CoDEX trial, intravenous dexamethasone was shown to shorten the ventilator-free days of patients with CARDS (70). The REMAP-CAP trial indicated that hydrocortisone contributed to improved organ support-free days within 21 days (71). Another retrospective study found that low-dose corticosteroid therapy may help to reduce the risk of in-hospital death in CARDS patients (72). The above studies indicated that the use of steroids was related to the reduced mortality in critically ill patients with COVID-19, and corticosteroids could be administrated in general treatment in CARDS patients (73). Nevertheless, another study found that patients with mild ARDS could not benefit form corticosteroids administration (74). Furthermore, specific virus types may lead to different responses for corticosteroids. Prior studies have found that corticosteroids were linked to delayed viral clearance in SARS and Middle East respiratory syndrome (MERS) (75,76), which increased concerns that corticosteroids might damage host response to COVID-19. In addition, patients with influenza pneumonia who received corticosteroids experienced increased mortality (77). In summary, further study is required to explore the harmful or beneficial effects of corticosteroids for this application (78). Furthermore, re-evaluation in combination with novel therapeutic strategy, such as new anti-viral therapies, immunomodulatory agents, and potential monoclonal antibodies (mAbs), may display considerable efficacy as well.

Anti-cytokine storm drugs

As the critical pathophysiologic progress in CARDS, the cytokine storm is triggered by the colossal release of pro-inflammatory cytokines, including IL-6, IL-1, TNF-α, and so on. This leads to a hyperactive and dysregulated immune reaction causing organ dysfunction. Therefore, the immunomodulatory drugs are of vital importance in anti-cytokine storm therapy.

Tocilizumab (TCZ), one of the most studied IL-6 inhibitors, has been identified to exert a great therapeutic effect in CARDS patients. A Chinese open-label, noncontrolled study showed that 21 severe COVID-19 patients who were treated with TCZ (400 mg IV infusion) harbored normal lymphocyte counts and improved oxygenation, manifesting the potential role of TCZ (79). Besides, Roche has approved TCZ to enter into a phase III RCT (COVACTA) in severe, hospitalized COVID-19 patients (80). Another IL-6 inhibitor, sarilumab, has been initiated clinical trials (NCT04315298, NCT04327388) in severe cases of SARS-CoV-2. Furthermore, novel mAb that inhibits IL-6 receptor (TZLS-501) is currently under investigation.

Anakinra (ANK) is an inhibitor of IL-1, which is considered a potential life-saving therapy for patients using non-invasive ventilation outside of the ICU (81). A small-scale respective study indicated that 55.6% of CARDS patients may benefit from high dose (100 mg every 6 h) subcutaneous ANK therapy (82). Especially in patients with elevated aminotransferases, ANK might become a potential alternative for non-response TCZ patients.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a cardinal role in inflammatory modulation. When binding to the receptor (GM-CSFR-α), various pro-inflammatory pathways are activated, inducing the release of pro-inflammatory cytokines (83). A single-

center, prospective cohort study found that mavrilimumab (an anti-GM-CSFR-α mAb) can improve the clinical outcome of patients with severe COVID-19 (84).

The functions of various IFN subtypes are different. In ARDS, IFN-γ has proinflammatory functions whereas IFN-b1a has antiviral and immunomodulatory functions (85,86). As such, the application of inhaled IFN-b1a formulation (SNG001) in CARDS is being evaluated in a clinical trial (NCT04385095).

Vitamin C and D might act as strong immunosuppressive agents in inhibiting cytokine release syndrome in COVID-19 (87). A retrospective study identified that high-dose (6 g IV infusion q12h D1 and 6 g qd for the following 4 days) vitamin C may decrease the death rate without adverse events in COVID-19 patients (88). In addition, the lack of vitamin D has been found to be associated with ARDS, due to lower 25(OH)D concentration (89). Currently, various RCTs utilizing either oral 25(OH)D or vitamin D are ongoing (90).

Mesenchymal stem cell (MSC) therapy

Violent cytokines release is attributed to T cells hyper-activation in CARDS patients, which lead to cytotoxic effects on the respiratory system (91). MSC could reduce the activation of T cells, B cells, natural killer (NK) cells, and dendritic cells (DC) by secreting cytokines. In addition, the induction of neutrophils, macrophages, and anti-inflammatory regulatory Treg cells is also the performance of MSC's immune modulation function. Currently, MSCs which are mainly derived from bone marrow (BM), umbilical cord (UC), adipose tissue (AD), and dental pulp (DP) have been involved in the clinical trials against COVID-19 in many countries (92,93). Preclinical research has identified that BM-MSCs have the regeneration and anti-inflammatory impact on damaged pulmonary alveolar and endothelial cells, through the release of extracellular vesicle (EV) and paracrine factors and transfer of mitochondria (94,95). Therefore, MSCs are shown to have the potential for treating severe COVID-19 cases. Previous studies have shown that MSC therapy improves the symptom and function of COVID-19 patients with ARDS and obtains a significant survival rate (95-97). Besides, exosomes originated from allogeneic BM-MSCs have been investigated to treat severely compromised COVID-19 patients in clinical trials (98-101). These results showed excellent ability and safety to downregulate cytokine storm, reconstitute immunity, and restore oxygenation.

Convalescent human plasma and intravenous immunoglobulin (IVIG)

Convalescent plasma enriched in antibodies is obtained from recovered COVID-19 patient, and then transfused to the infected patients. One study reported four of five severe COVID-19 cases who were transfused with convalescent plasma resolved the symptoms of CARDS at 12 days after transfusion (102). However, a Chinese study revealed that convalescent plasma therapy did not achieve a statistically significant clinical improvement within 28 days (103). Although in August 2020, the Food and Drug Authority (FDA) approved the use of convalescent plasma for the treatment of critically ill COVID-19 patients (104), this therapy still needs further research. In terms of IVIG, previous evidence has suggested that a high dose of IVIG therapy should be considered in patients with severe COVID-19 (105). Furthermore, the National Health Service (NHS) specialty guideline also recommended the use of IVIG for the treatment of COVID-19 patients with sepsis (106); IVIG is considered an important therapeutic approach.

Advanced potential therapy

Repositioning drugs

Currently, some advanced potential drugs have emerged to treat CARDS, which are mainly inferred from the mechanism of action with limited supporting clinical evidence. However, these therapies may provide a novel direction for developing repositioning drugs which could fight CARDS.

Opioids

Although opioids are most exploited in the analgesic aspect, they could also exert triple effects in combating COVID-19. The benefits of utilizing opioids contain addressing the unfavorable side-effects [cough (107) and dyspnea (108)], overcoming the virus infection cycle (inhibit lysosomal acidification) (109), and the host reactions to the virus-elicited pathogenesis (anti-excessive inflammation) (110). In addition, hydromorphone and oxycodone could alleviate the subjective perception of CARDS as well as reduce anxiety effects (111,112). Therefore, further investigation is warranted to evaluate the long-term therapeutic effects of opioids.

Radiotherapy (RT)

The evidence in literature has revealed that RT may be

effective for mitigating CARDS (113). Firstly, low-dose radiation (LDR) is conducive to decelerate viral loading and replication (114) in the pulmonary epithelial cells by oxygen metabolism. In addition, LDR could enhance the recruitment of circulating immune cells and further promote the antiviral environment (115). As for the LDR, a single total dose of 0.3–0.5 Gy would be of great benefit for CARDS patients (116). However, the optimal dose of RT should be assessed carefully and repetitively in the future clinical trials.

Poly ADP-ribose polymerase (PARP) inhibitors (PARPis)

PARPs take part in various cellular processes, containing cell death, autophagy, antiviral response, and immune function. Some researchers (117,118) have verified that PARPi could decrease the critical interleukins in COVID-19-induced cytokine storm. Furthermore, PARPis has the ability of counteracting cell death induced by SARS-CoV-2 and inflammation and supporting cell survival (119). The benefits of PARPis have been supported by great therapeutic effects in animal models of VILI and ARDS (120,121). Thus, PARPis may potentiate the effectiveness of anti-cytokine storm therapy (122-124) and would be beneficial for SARS-CoV-2 patients.

Prognosis

Mortality and survival

Although most COVID-19 patients experience mild symptoms, 19% could present with intractable conditions and develop severe or fatal symptoms, particularly CARDS (4). In developed countries, the mortality rate of cards can reach 30–50% (125-129), which is consistent with the mortality from non-COVID ARDS in the ICU. Moreover, in some cases, the mortality rate of patients with CARDS can reach 70% (130). In addition, a study showed that the 90-day mortality rate of CARDS increased with the severity of CARDS (30%, 34%, and 50% for mild, moderate, and severe cards, respectively) (125). Another unfortunate reality is that patients with CARDS who are accompanied with acute kidney injury (AKI), acute heart injury, and septic shock will face significantly reduced mortality (131).

Sequelae

Patients who have survived CARDS may further experience many medical consequences post intensive care therapies. Most common long-term consequences of CARDS include impaired weaning from mechanical ventilation, ventilator-diaphragmatic interactions, ICU-acquired weakness (132-134), consequences from other organ injury (131), other neuromuscular disorders (e.g., dysphagia) (135,136) and/or thromboembolic complications (137). All the above "sequelae" of CARDS not only damage the survival and health of patients, but also place a huge burden on the social medical system. Hence, it is necessary to identify biological markers that predict individual prognosis.

Prognosis biomarkers

The most common combined biomarkers that have been used are age, lymphocyte percentage, monocyte percentage, CRP, procalcitonin, and serum albumin. These are regarded as independent predictors of a more severe illness course (138,139). In addition, based on the pathogenesis of CARDS: endothelial injury, epithelial injury, inflammatory cascade, and coagulation cascade (140), there are some the most commonly promising prognostic biomarkers: lactate dehydrogenase [LDH; weakens the immune response to viral infection (141)]; ferritin (142); D-dimer (143); proinflammatory cytokines (they often are measured as part of a panel and have insufficient specificity to serve as a stand-alone biomarker (144,145); nicotinamide phosphoribosyltransferase (eNAMPT) (146); soluble intercellular adhesion molecule-1 (sICAM-1) [an early pulmonary endothelial injury maker of CARDS (147)]; angiopoeitin-2 (Ang-2) in plasma, and receptor for advanced glycation end products (RAGE) in plasma (148).

Summary

The COVID-19 is an unprecedented pandemic and can lead to fatal clinical outcomes, particularly CARDS. Researchers have made great efforts to improve the prognosis of severe COVID-19 and reduce the mortality caused by CARDS. Among them, a large number of studies have attempted to determine whether CARDS is "typical" or "atypical" ARDS. As of the time of writing,

we have delineated the pathophysiological mechanism, manifestations, diagnosis, treatment, management, and prognosis biomarkers of CARDS based on the past 1-year development of this disease, and further highlighted and elucidated the differences between typical ARDS and atypical CARDS from all of the above aspects. Despite the differences between the CARDS and ARDS, in addition to the treatment of antivirals, clinicians should continue to follow the accepted evidence-based framework for managing all ARDS cases, including CARDS. In fact, our study is still not comprehensive, such as failing to explain the mechanistic differences between CARDS and ARDS in more depth. However, we still help clarify the homogeneity and heterogeneity between CARDS with other cause ARDS, which may provide direction for the future basic research and help to optimize the clinical management framework of this disease.

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Footnote

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