# A Systematic Review of Coronavirus Disease 2019 with Respiratory Distress Syndrome in Adult: Focus on Risk Factors, Mechanism, Diagnosis, and Treatment

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**Abstract**

**Context:** Coronavirus disease 2019 (COVID-19) is a newly discovered disease, caused by SARS-CoV-2 and currently has become a pandemic. Acute respiratory distress syndrome (ARDS) is the most common complication in COVID-19. There were numerous conflicting results among articles related to it. The aim of this study is to ascertain the most compelling evidence about ARDS in COVID-19.

**Evidence Acquisition:** This systematic review was registered in PROSPERO (CRD42020180379). A systematic search was conducted in PubMed, PubMed central, and Google Scholar on April 16, 2020. Two reviewers independently searched and selected the articles. The risk of bias was evaluated using the Newcastle-Ottawa Quality assessment tool.

**Results:** A total of 1,647 articles were screened, 9 articles were included. Patients were classified as having various degrees of ARDS, the diagnosis of COVID-19 was confirmed by PCR nasopharyngeal swab. Risk factors of ARDS in COVID-19 reported were older age, male gender, and pre-existing medical conditions. Cytokine storm was thought to play a role in the mechanism of ARDS. The main treatment for COVID-19 was supportive and symptomatic. To date, there is no antiviral treatment recommended for COVID-19 and the given treatment for ARDS in COVID-19 was similar to other pneumonia-induced ARDS. No additional therapy specific for ARDS in COVID-19 has been proposed.

**Conclusion:** Our synthesis of the literature showed that there was no good evidence in the mechanism and treatment of ARDS. Further translation research in the mechanism of ARDS and continuing with clinical trials evaluating drug efficacy for ARDS in COVID-19 is needed.

## Introduction

Since December 2019, the world has been introduced to a new type of viral pneumonia, Coronavirus disease 2019 (COVID-19).[1] Out of all complications, acute respiratory distress syndrome (ARDS) was the most prevalent.[1–5] Study from Xiaobo Yang, et al reported that 67% of critically ill COVID-19 patients had ARDS.[2] ARDS increased the need of mechanical ventilation and intubation, although some studies also suggested the usage of extracorporeal membrane oxygenation (ECMO). In addition, ARDS increased mortality risk; most patients who died from COVID-19 developed ARDS.[2] Recently, many articles have been published in relation to ARDS in COVID-19. There is still conflicting data about the risk factor, mechanism, diagnosis, and treatment of ARDS in COVID-19 since its outbreak.

The aim of this systematic review is to summarize the literature and evaluate the strength of the evidence of risk factor, mechanism, diagnosis, and treatment of COVID-19 and ARDS.

## Material and Methods

### Search Strategy

This systematic review was registered at PROSPERO (International database of prospectively registered systematic reviews) (CRD42020180379) [6]

A literature search was performed on electronic databases, including PubMed, Pubmed Central and Google Scholar. A literature search was conducted on April 16, 2020, using keywords listed in Table 1. The results, obtained from the database corresponding to clinical questions using Boolean operators, are presented in Table 1.

The literature search process was performed within the limits of the literature research, whereas the titles and abstracts were selected from each database. Studies were included in this review if they met the following inclusion criteria: representation for clinical questions (P: adult with COVID-19; I: adult with respiratory distress syndrome; C: adult without respiratory distress syndrome; O: risk factors, mechanism, diagnosis, and treatment), type of the study was either a review article, case report, observational study and clinical trial, and if the full-text article was available. The diagnosis of COVID-19 made by molecular test using reverse transcription polymerase chain reaction (RT-PCR) as the golden standard. Sample must be obtained from nasal and throat swab or other respiratory tracts. The outcome may be within any time period. Studies that included pregnant women population or articles that were not in English were excluded.[7]

Two independent reviewers (AK and CJ) selected the articles, extracted the data, and analyzed the data. Any discrepancies were resolved by consensus between the reviewers or after discussion with a third author (DAH). The reviewers evaluated the title and abstract for all studies that were identified through the PRISMA search strategy. Full texts were evaluated when there was insufficient information in the title and abstract to make decisions about inclusion and exclusion. References in reviewed and excluded articles were examined to identify studies that may not have been identified through the primary search strategy. The search was limited to English. A list of potential studies for inclusion in the systematic review was generated through the process.

### Data Extraction

Extracted data included details regarding authors, last five years of publication, country of study population, inclusion/exclusion criteria (patient characteristics), and description of outcomes. Data were also extracted regarding COVID-19 (confirmation cases by PCR swabs), study outcomes (e.g., risk factors, mechanism, diagnosis, and treatment) and secondary outcomes (survival, length of stay, and ventilator dependence).

Multiple article checks were performed in the three databases. The appropriate study

was read in full paper and appraised. A critical appraisal was made based on the Oxford's Center for Evidence-Based Medicine assessing the validity, importance, and applicability of each article. A flow diagram describing the study selection process is shown in Figure 1. [8,9]

### Outcome Definitions

Primary outcomes include risk factors, mechanism, diagnosis, and treatment. The secondary outcomes consist of survival, length of stay, and ventilator dependence.

### Quality Assessment

The Newcastle-Ottawa Quality (NOQ) assessment of observational trials was used to measure the risk of bias in this systematic review. Two independent researches (AK and DAH) assessed methodological quality and standard of outcome reporting in the included studies. Disagreement between was solved by consensus and if no consensus exists, the opinion of a third reviewer (CJ) was sought. The quality of evidence assessed using the GRADE (Cochrane Group) analysis of findings was not done. [10,11]

## Results

### Literature search

A total of 1,663 articles were identified through the search strategy. Figure 1 presents the PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[9] After duplicates were removed, the two primary reviewers (AK and CJ) screened titles and abstracts for 1,647 articles. The remaining 54 full texts were reviewed for its eligibility. Most articles were excluded because they did not include information on outcomes selected for our reviews or did not include comparison groups. Ultimately, 9 articles were selected[5,12–19] with a total of 1,121 patients. Overview of the included studies were presented in Table 2.

<<Figure 1 here>>

### Primary Outcomes

### Risk Factors

Risk factors of developing ARDS in COVID-19 are age, particularly those who are older than 65 years old, male gender, patients' symptoms on arrival including higher temperature and dyspnea, pre-existing medical conditions such as hypertension, diabetes, other cardiovascular diseases, and lung disease. Some laboratory values were also identified to be a risk factor, namely lymphocytopenia, elevated total bilirubin, urea, D-dimer, interleukin-6 and neutrophilia.[2,5,15,16,18–20] Further information regarding risk factors are listed in Table 2. It is important to note that patients who developed ARDS and did not receive antiviral therapy were treated with methylprednisolone because they had higher score of Pneumonia Severity Index (PSI) and had a significant elevation in some laboratory tests compared to patients without ARDS.[5]

### Mechanism/ Pathophysiology

The coronavirus enters the body by binding to angiotensin converting enzyme 2 (ACE2) receptors. This receptor is located in many organs of the body, such as lung, heart and kidney.[13] The immune system is needed to eradicate virus from the body, but if the immune mediators are released uncontrollably, it can lead to organ damage.[15,19] Cytokine is one of the immune mediators; its level is highly elevated in COVID-19 patients. [14,19] This is also known as cytokine storm. Cytokine storm was thought to play a role in the development of ARDS in COVID-19 patients.[5,14,16,19]

A lung pathological study from ARDS secondary to COVID-19 displayed pulmonary edema and hyaline membrane formation.[16] Another study also reported that patients also established diffuse alveolar damage accompanied by cellular fibromyxoid exudating in their lungs.[20]

## Diagnosis

An arterial blood gas (ABG) analysis should be done to diagnose ARDS.[13,16,20] Based on WHO definition, ARDS is categorized into three classifications, based on the degree of hypoxemia: mild (200 mm Hg < $PaO_2/FIO_2$ ≤ 300 mm Hg), moderate (100 mm Hg < $PaO_2/FIO_2$ ≤ 200 mm Hg), and severe ($PaO_2/FIO_2$ ≤ 100 mm Hg).[5,14] Beside ABG analysis, a study from Yingxia Liu, et al used Murray score to assess the degree of lung injury in ARDS. The greater the score, the more severe the ARDS.[13]

## Treatment

The main treatment for COVID-19 is supportive and symptomatic by hydration and nutrition. Monitoring vital signs, oxygen saturation and intake-output balance are also needed.[2,16] To date, there is no specific antiviral treatment recommended for COVID-19, but most of the studies used oseltamivir and lopinavir/ritonavir.[2,5,13–16] Empirical antibiotics were also administered to patients in some studies.[5,14,16]

Regarding the management of ARDS in COVID-19 patients, identifying those who have high risk to develop ARDS and monitoring them closely were the most important. For monitoring, ICU admission was needed.[5,14] In order to suppress immune response, administration of steroids and even anti-IL-6 could be done.[2,5,14–16,19,20] Oxygen therapy was required and could be given through nasal prongs, face mask and high flow nasal cannula. Mechanical ventilation, noninvasive or invasive, might be needed for patients in critical condition. Prone position was also recommended to aid patients with ARDS. Extracorporeal membrane oxygenation (ECMO) might also be given to patients with refractory hypoxemia.[2,5,14–16,18–20] Table 2 shows the managements that had been done or recommendations from various studies.

## Secondary outcomes

According to Chaomin Wu, et al study, 44 (52.4%) out of 84 patients[5], 26 (74.3%) out of 35 patients from Xiaobo Yang, et al study[2], six (50%) out of 12 patients from Chaolin Huang, et al study[14] and all 113 (100%) patients in Tao Chen, et al study[16] who developed ARDS did not survive. Patients with ARDS secondary to COVID-19 had higher mortality rates, especially those with advanced age. Not only increasing the mortality rate, ARDS also increased the burden on healthcare workers due to the prolonged length of hospital stays, and most patients who develop ARDS needed ICU admission and mechanical ventilation support.[5,14] Similar findings were found in one study from Yingxia Liu, et al: six (100%) out of six patients who developed ARDS required mechanical ventilation[2,5,13] and intubation.[18]

## Quality Assessment

Table 3 summarizes the Newcastle-Ottawa Quality (NOQ) assessment of observational trials results for studies included in the review. No studies were rated “good”; all studies were rated “poor”.[2,5,14–16,20] The GRADE analysis was not done because this study will not continue to a meta-analysis study.

## Discussion

This systematic review evaluated ARDS in COVID-19 infection. An important finding was that male patients older than 65 years old and those with preexisting medical condition, mainly hypertension, diabetes, chronic obstructive pulmonary disease and cardiovascular disease, seem to be at a higher risk of developing ARDS.[2,5,15,16,18–20] These findings were similar to the other meta-analysis about the severity factors of COVID-19. Study from Chaomin Wu, et al also analyzed the symptoms on the arrival of patients with ARDS and found that those who suffered from higher fevers (≥39°C) and had dyspnea had higher risk.[5] Some laboratory values could also be a predictor for ARDS, but from a total of 9 studies, only two studies analyzed this aspect.

Lymphocyte count were found to be lower according to Chaomin Wu, et al and Yulong Zhou study, with 0.67 (0.49-0.99) x $10^9$/L and 0.65±0.339 x$10^9$/L, respectively.[5,15]

Immune system was figured out to play a major role in ARDS pathogenesis. It was

thought that there were two phases of immune response produced by SARS-CoV-2 infection: non-severe and severe phase (Figure 2). When the severe phase took place, it would induce cytokine storm.[21] Cytokine storm would cause more damage and eventually ARDS to occur.[5,15,16,19] Findings behind the mechanism of ARDS in COVID-19 patients were based on general knowledge and laboratory tests. Study from Chaomin Wu, et al postulates cytokine storms based on neutrophilia. [5] On the other hand, cytokine test was done by Tao Chen, et al.[16] Some studies also reported elevation of inflammation predictors and cytokines which supported the idea of cytokine storm.[1,13–15]

<< Figure 2 here>>

Even though some laboratory tests were elevated in patients who subsequently developed ARDS, the diagnosis of ARDS was still made based on the ABG analysis.[5,13,16,20] Aside from ABG analysis, study from Yingxia Liu, et al also used Murray score in order to assess the ARDS severity. It was found that the viral load was associated with the degree of severity.[13,22] One subject, a 63 year old male from Yingxia Liu, et al's study developed a very high viral load and suffered from fulminant myocarditis.[13] Thereby, this scoring might be helpful for assessing those who need closer monitoring.

Mainstay management of ARDS in COVID-19 was to identify the high risk groups and monitoring and oxygen support was also an important key in managing patients.[2,5,14,15,18–20] A study also suggested the use of ACE inhibitor or angiotensin receptor blocker drugs.[13] Most studies in this systematic review suggested the use of immunosuppressants, but there was no detailed recommendation regarding the dose and length of drug usage.[2,5,14–16,19,20] Study from Dennis McGonagle, et al also stated that IL-6 was greatly induced by SARS-CoV rather than by influenza A virus and human parainfluenza virus type 2. Viral replication might be increased or suppressed by IL-6, depending on the virus.[23] It was not yet clear whether IL-6 suppresses or initiates further viral replication in COVID-19. With regards to steroids use, some studies, international consensus and WHO did not recommend the use of glucocorticoids in ARDS patients.[24,25] Many articles discussed the management of ARDS, but none of them provided satisfactory evidence and recommendations, thus further study is needed.

ARDS patient survival was poor.[2,5,14,16] Even in Tao Chen, et al study, all ARDS patients died. However, sepsis was also developed, and it might be possible that the poor survival rate was due to the development of sepsis.[16] It was necessary to monitor those with ARDS and who were in more critical condition. Hence the hospital stay duration was longer and mechanical ventilation might be needed in ARDS patients.[2,5,13,14,26] The inflammatory markers to predict severe COVID-19 have been reported, for instances C-reactive protein, procalcitonin, lactate dehydrogenase, D-Dimer, and albumin.[27] To date in the recent meta-analysis, many efforts have been done to control the disease such as Remdesivir[28], Lopinavir/ritonavir[29] Dexamethason[30], and Tocilizumab[31-32]. Patients with comorbidities should continue their therapy.[33-35]

The limitation of this study is that there are no sufficient research references marked good. All studies included in our analysis were rated poor based on Newcastle-Ottawa Quality assessment. This was due to the comparability of the cohort studies included were scored zero, indicating poor quality studies. Only one study provided exposed and non-exposed table & discussion[15] but neither age nor sex and other confounders were found statistically significant, while other studies compared directly the population of the outcomes. Hence, they are not in accordance with the design study. This could be explained due to the limited time to collect and analyze the study about the newly discovered disease, COVID-19. As a result, this systematic review lacks satisfactory evidence. We strongly suggest further research about ARDS in COVID-19 adjusting to the

appropriate steps based on the used study design to produce a better-quality study. The overall included studies lacked evidence regarding the management of COVID-19 with ARDS. We suggest that future research and clinical trials focusing on this aspect provide better evidence in the future.

## Conclusion

This systematic review evaluation consisted of risk factors, mechanisms, diagnosis, and treatment of ARDS related to COVID-19. The age, gender, comorbidities, presenting symptoms and some laboratory values were associated with higher risk of developing ARDS in COVID-19. Our synthesis of the literature shows that there is no good evidence in the mechanism and treatment of ARDS. Future translation research is needed to explore more in the mechanism of ARDS, evaluating the key player between inflammation, thrombosis, hypoxemia, and organ dysfunctions. Furthermore, clinical trials are needed to evaluate the drug or drug combinations targeting the key factors of ARDS.

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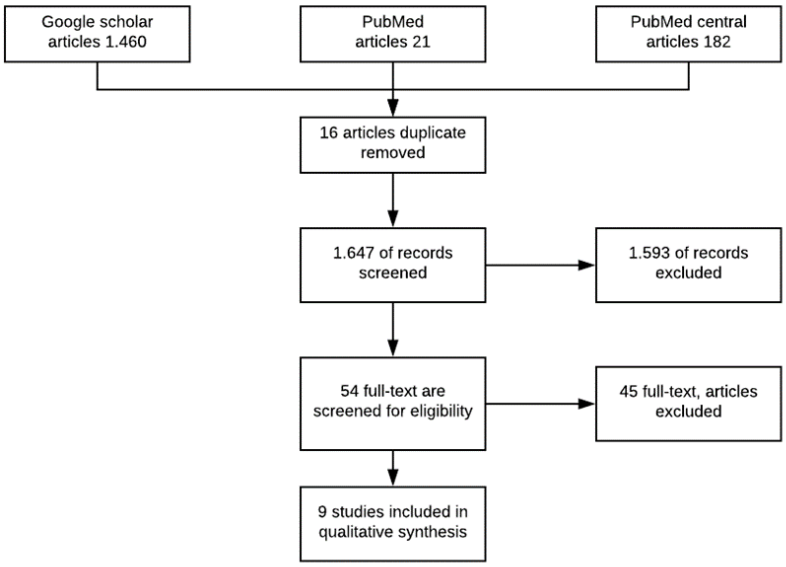


Figure 1. PRISMA Diagram

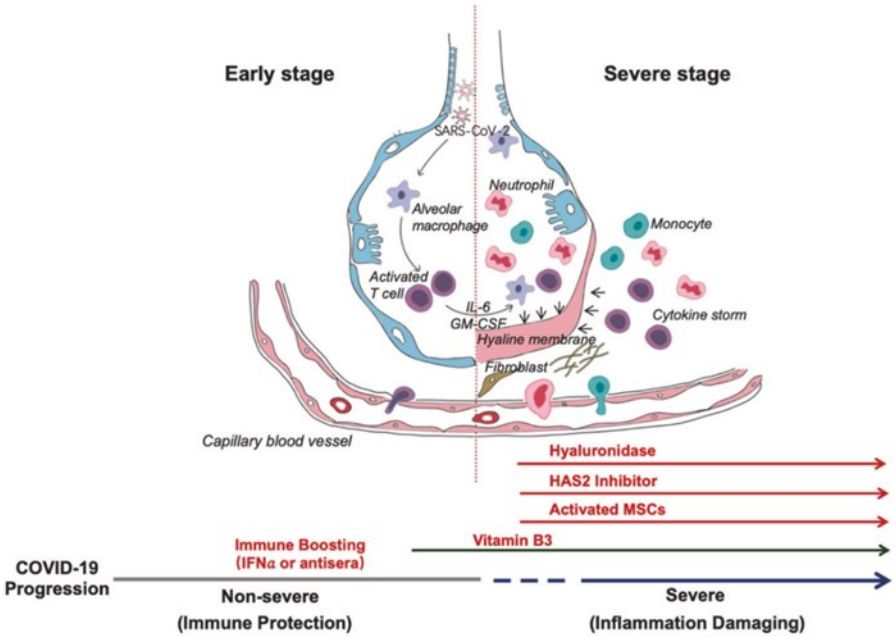


Figure 2. Immune Response Phase

Table 1. Literature search strategy

| Database | Keyword | Result |
|---|---|---|
| PubMed | ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("respiratory distress syndrome, adult"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "adult respiratory distress syndrome"[All Fields] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "respiratory distress syndrome, adult"[All Fields]) | 21 |
| Pubmed central | ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("respiratory distress syndrome, adult"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "adult respiratory distress syndrome"[All Fields] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields] AND "adult"[All Fields]) OR "respiratory distress syndrome, adult"[All Fields]) | 182 |
| Google scholar | COVID-19 AND Respiratory distress syndrome AND risk factor AND mechanism AND treatment | 1460 |

Table 2. Characteristics of included studies

| Author | Participants | Study type | Risk factor | Mechanism | ARDS Diagnosis | Treatment | Reference |
|---|---|---|---|---|---|---|---|
| Chaomin Wu, et al | 201 | Retrospective cohort | Older age<br>Higher temperature and dyspnea on admission<br>Comorbid<br>Elevated total bilirubin, urea, D-dimer, interleukin-6<br>Higher neutrophil count<br>Lower total lymphocyte count | Cytokine storm and cellular immune response | - | Oxygen support<br>Empirical antibiotics<br>Antiviral<br>Antioxidant therapy: glutathione and N-acetyl-L-cysteine<br>Methylprednisolone<br>Immunomodulators | [5] |
| Xiaobo Yang, et al | 52 | Retrospective cohort | Age >65 years old<br>Male | - | - | Mechanical ventilation<br>Prone position<br>Antiviral<br>IV glucocorticoids | [2] |
| Yingxia Liu, et al | 12 | Retrospective cohort | - | - | Arterial blood gas analysis<br>Murray score to assess the severity of lung injury in ARDS | Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker may be used to treat COVID-19 | [13] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chaolin Huang, et al | 41 | Prospective cohort | - | - | - | Oxygen therapy<br>ECMO for refractory hypoxemia<br>Empirical antibiotic<br>Corticosteroids | [14] |
| Yulong Zhou, et al | 17 | Retrospective cohort | Lower total lymphocyte count | - | - | Oxygen support<br>Antiviral<br>Corticosteroid | [15] |
| Tao Chen, et al | 274 | Retrospective cohort | Age >60 years old<br>Male<br>Comorbid (hypertension in particular) | Pulmonary edema with hyaline membrane formation<br>Cytokine storm | Arterial blood gas analysis | Oxygen support, if fail, mechanical ventilation<br>ECMO<br>Antiviral<br>Antibiotics<br>Glucocorticoid | [16] |
| Xiao Tang, et al | 148 | Retrospective case-control | Older age | Diffuse alveolar damage, fibromyxoid exudation | Arterial blood gas analysis | Antiviral<br>Oxygen support<br>Mechanical ventilation<br>ECMO<br>Glucocorticoids<br>Immunoglobulin<br>Chinese traditional medicine | [20] |
| Wenlong Yao, et al | 202 | Retrospective cohort | Age ≥ 65 years old<br>Male | - | - | Oxygen therapy<br>Intubation<br>Prone ventilation | [18] |
| Wen Jun Tu, et al | 174 | Retrospective cohort | Older age<br>Male<br>Comorbid | Interferon-γ-related cytokine storm | - | Methylprednisolone<br>Invasive mechanical ventilation<br>Antiviral<br>Tocilizumab | [19] |

Table 3. Newcastle-Ottawa quality assessment of observational trials

| First author, year | Study design | Selection | Comparability | Exposure/Outcome | Total score | Result |
|---|---|---|---|---|---|---|
| Chaomin Wu, et al. 2020 | Cohort | *** | - | *** | 6 | Poor |
| Xiaobo Yang, et al., 2020 | Cohort | **** | - | *** | 7 | Poor |
| Chaolin Huang, et al., 2020 | Cohort | *** | - | *** | 6 | Poor |
| Yulong Zhou, et al., 2020 | Cohort | **** | - | * | 5 | Poor |
| Tao Chen, et al., 2020 | Cohort | ** | - | ** | 4 | Poor |
| Xiao Tang, et al., 2020 | Case-control | *** | - | *** | 6 | Poor |