# COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS

COVID-19 ARDS is a predictable serious complication of COVID-19 that requires early recognition and comprehensive management

"This disease is still too strange to us, and there are too many doubts", says Dr Ling Qin (LQ), after reviewing more than 400 patients with coronavirus disease 2019 (COVID-19) pneumonia in Wuhan Union Hospital, China. COVID-19 is a novel disease. We are familiar with acute respiratory distress syndrome (ARDS); however, when it occurs as part of COVID-19, it has different features and there remain unanswered questions.

So if someone has COVID-19 ARDS, how does it compare and contrast with ARDS from other causes? To answer this question we provide a summary of the published literature (based on a PubMed search using the terms "COVID-19" and "ARDS", 17 April 2020) and current clinical experience from managing patients with COVID-19 ARDS in Singapore (SHP) and Wuhan (LQ).

Severe COVID-19 represents viral pneumonia from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to ARDS. Its manifestations can be viewed as a combination of the two processes, namely viral pneumonia and ARDS. COVID-19 is a novel disease recognised initially in Wuhan, China, in December 2019, and is now pandemic. It is likely caused by zoonotic spillover of a β-coronavirus type 2b that is now transmitted between humans. Along with the other serious coronavirus infections of severe acute respiratory syndrome and Middle East respiratory syndrome, which also cause ARDS, COVID-19 represents an ongoing global threat as this virus family has the potential to mutate and infect non-immune populations. Australia's living guidelines provide the latest recommendations and evidence.[1]

## Diagnosis

SARS-CoV-2 infection can be confirmed by positive detection of viral RNA in nasopharyngeal secretions using a specific PCR test. COVID-19 illness can be confirmed by a consistent clinical history, epidemiological contact, and a positive SARS-CoV-2 test. COVID-19 ARDS is diagnosed when someone with confirmed COVID-19 infection meets the Berlin 2012 ARDS diagnostic criteria[2] of (i) acute hypoxaemic respiratory failure; (ii) presentation within 1 week of worsening respiratory symptoms; (iii) bilateral airspace disease on chest x-ray, computed tomography (CT) or ultrasound that is not fully explained by effusions, lobar or lung collapse, or nodules; and (iv) cardiac failure is not the primary cause of acute hypoxaemic respiratory failure.

ARDS is underdiagnosed in intensive care settings.[3] ARDS develops in 42% of patients presenting with COVID-19 pneumonia, and 61–81% of those requiring intensive care.[4] COVID-19 ARDS follows a predictable time course over days, with median time to intubation of 8.5 days after symptom onset in Singaporean patients.[5] This is similar to previous reports where ARDS developed at day 8 or 9 after symptom onset. It is therefore important to monitor patients for the development of ARDS as their COVID-19 infection progresses. Respiratory rate and $SpO_2$ are two important parameters for judging patients' clinical condition and allowing early recognition of ARDS. A patient who fits any one of the following conditions may have severe disease and require further evaluation: respiratory rate ≥ 30 breaths/min; $SpO_2$ ≤ 92%; and $PaO_2/FiO_2$ ≤ 300 mmHg.

Blood tests can also be helpful. In Singapore, it was noted that raised C-reactive protein levels and blood neutrophil counts along with lymphopenia were more common in patients requiring invasive mechanical ventilation for COVID-19 ARDS.[5]

## Lung pathology

ARDS causes diffuse alveolar damage in the lung. There is hyaline membrane formation in the alveoli in the acute stage, and this is followed by interstitial widening and by oedema and then fibroblast proliferation in the organising stage. COVID-19 ARDS causes the typical ARDS pathological changes of diffuse alveolar damage in the lung.[6,7] As patients move through the course of their illness, the longer term outcomes of ARDS are being reported, with lung fibrosis appearing as part of COVID-19 ARDS.[8,9] A study reported that 17% of patients had fibrous stripes in chest CT scans,[9] and considered that the fibrous lesions may form during the healing of pulmonary chronic inflammation or proliferative diseases, with gradual replacement of cellular components by scar tissues.

## Thrombosis

Pulmonary thrombosis is common in sepsis-induced ARDS. Coagulation dysfunction appears to be common in COVID-19, and is detected by elevated D-dimer levels. In fatal cases there is diffuse microvascular thrombosis, suggesting a thrombotic microangiopathy, and most deaths from COVID-19 ARDS have evidence of thrombotic disseminated

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intravascular coagulation.[10] This may explain some of the atypical or unexpected manifestations seen in the lung, such as dilated pulmonary vessels on chest CT, and episodes of pleuritic pain. Vascular enlargement is rarely reported in typical ARDS, yet was seen in most cases of COVID-19 ARDS.[9]

## Mortality

COVID-19 ARDS appears to have worse outcomes than ARDS from other causes. The intensive care unit and hospital mortality from typical ARDS are 35.3% (95% CI, 33.3–37.2%) and 40.0% (95% CI, 38.1–42.1%), respectively.[3] For COVID-19 ARDS, mortality ranged between 26% and 61.5% if ever admitted into a critical care setting, and in patients who received mechanical ventilation, the mortality can range between 65.7% to 94%.[4] Risk factors for poor outcomes include older age; presence of comorbidities such as hypertension, cardiovascular disease and diabetes mellitus; lower lymphocyte counts; kidney injury; and raised D-dimer levels. Death from COVID-19 ARDS is due to respiratory failure (53%), respiratory failure combined with cardiac failure (33%), myocardial damage and circulatory failure (7%), or death from an unknown cause.[4]

## Radiology

The radiology of ARDS is distinctive, yet COVID-19 pneumonia appears to have unique features. This likely results from the co-occurrence of viral pneumonia and ARDS, and allows radiologists to be fairly specific in diagnosing COVID-19 pneumonia. The most discriminating features for COVID-19 pneumonia in China compared with viral pneumonia in the United States included a peripheral distribution of opacification (80% *v* 57%; $P < 0.001$), frosted glass opacities (91% *v* 68%; $P < 0.001$), and vascular thickening or enlargement (58% *v* 22%; $P < 0.001$).[11]

These imaging features appear to be typical for COVID-19 pneumonia and can be helpful in early screening of highly suspected cases and in evaluation of the severity and extent of disease. As COVID-19 lung disease progresses, the lesions are more likely to be bilateral, lower lung predominant and multifocal. They often have the appearance of rounded opacities, termed "COVID balls". With the development of ARDS, the extent of lung involvement increases, and there is a consolidative component.[12] The opacities resolve with recovery from COVID-19;[13] however, with ARDS, the lesions increase in their extent and density, and evolve to fibrotic bands.

## Ventilation

The strategy of breathing support is very important in treating COVID-19 ARDS, as is the case with typical ARDS caused by other pathogens.[14] The key elements are:

- use oxygen by nasal cannulae to achieve $SpO_2 > 92\%$;
- use of high flow nasal oxygen is controversial and highly dependent on the treatment location;
- avoid non-invasive ventilation;
- prone ventilation appears to be beneficial; and
- consider extracorporeal membrane oxygenation for rescue.

Because of concerns about viral transmission to other patients and health care workers,[15] the use of high flow nasal oxygen and non-invasive ventilation (such as bi-level positive pressure ventilation) for COVID-19 ARDS is highly dependent on the health care setting. Australian COVID-19 guidelines[1] strongly recommend against the use of high flow nasal oxygen in emergency departments, but provide a strong recommendation for its use in negative pressure single rooms. Non-invasive ventilation may be used in negative pressure rooms with appropriate viral transmission precautions.[1] Clinical experience has found inconsistent benefit from non-invasive ventilation and there is concern about aerosol generation and increased risk of viral transmission. Prone ventilation appears to be beneficial for COVID-19 ARDS.[1] Placing a person in prone position promotes more homogenous aeration of the lung in ARDS and can improve oxygenation. While prone ventilation is used in only about 16% of patients with typical ARDS,[3,16] in COVID-19 it is being used successfully earlier in the course of ARDS, and suggested use is for > 12 hours per day.[16] Venovenous extracorporeal membrane oxygenation can be used as rescue for mechanically ventilated adults with COVID-19 and hypoxaemia that persists despite optimised ventilation, use of rescue therapies and prone ventilation.

Among critically ill patients treated in Wuhan, prone ventilation and extracorporeal membrane oxygenation treatment were not found to be as effective as for ARDS caused by other pathogens. Possible reasons include:

- COVID-19 pneumonia was still progressing and was not under control;
- lung lesions were not completely gravity-dependent under ultrasound, so the effect of the prone position was limited;
- the patient's immune status was not restored, and a secondary hospital-acquired infection worsened the condition; and
- when case numbers are high from the epidemic, the management mode and human resource arrangement of the isolation wards still need to be discussed and strengthened.

Anecdotal observations in Singapore (SHP) and investigations in the Netherlands[17] suggested that patients ventilated for COVID-19 ARDS tended to have plateau pressures < 30 $cmH_20$ and driving pressures < 15 $cmH_20$ despite high oxygen requirements. The lung protective ventilation strategy used in typical ARDS involves a low tidal volume (6 mL/kg) and higher positive end expiratory pressure targets. For

COVID-19 ARDS, a change to more generous tidal volume targets allowing up to 8 mL/kg and lower positive end expiratory pressure levels is suggested to prevent patient self-inflicted lung injury.

## Adjunct treatment

In typical ARDS, continuous neuromuscular blocking agents, high dose corticosteroids and recruitment manoeuvers were the most frequently used adjunctive therapies.

In COVID-19 ARDS, the evidence for systemic steroids is still scarce and they are only recommended in patients with concomitant shock which has been unresponsive to vasopressors. There are concerns that steroids may increase viral shedding and possibly lead to a higher mortality rate.

## Antiviral therapy

Many patients with COVID-19 receive antiviral or immunosuppressive therapy. In Australia, the National COVID-19 Clinical Evidence Taskforce[1] recommends administering antiviral medications or other disease-modifying treatments in the context of clinical trials. Singapore was using empiric lopinavir–ritonavir plus subcutaneous interferon-β 1b initially, but is now randomising patients to receive remdesivir. In Wuhan, a broad range of antiviral and immune therapies are being used. All patients also received treatment with Chinese medicine.

COVID-19 ARDS is a predictable serious complication of COVID-19 that requires early recognition and comprehensive management. Research programs such as the Medical Research Future Fund 2020 Respiratory Medicine Clinical Trials Research on COVID-19 grant opportunity are required to answer the important questions that remain about therapies for COVID-19 ARDS.

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