Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from COVID-19 Infection

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Abstract

The coronavirus disease 2019 (COVID-19) outbreak that started in Wuhan, Hubei province, China in December 2019 has now extended across the globe with >100,000 cases and 3,000 deaths reported in 93 countries as of 7 March 2020. We report a case of COVID-19 infection in a 64-year-old man who developed rapidly worsening respiratory failure and acute respiratory distress syndrome (ARDS) that required intubation. As the clinical spectrum of COVID-19 range widely from mild illness to ARDS with a high risk of mortality, there is a need for more research to identify early markers of disease severity. Current evidence suggests that patients with advanced age, pre-existing comorbidities or dyspnoea should be closely monitored, especially at 1–2 weeks after symptom onset. It remains to be seen if laboratory findings such as lymphopenia or elevated lactate dehydrogenase may serve as early surrogates for critical illness or markers of disease recovery. Management of ARDS in COVID-19 remains supportive while we await results of drug trials. More studies are needed to understand the incidence and outcomes of ARDS and critical illness from COVID-19, which will be important for critical care management and resource planning.

Key words: Acute Respiratory Distress Syndrome, COVID-19, Critical illness, Intensive Care, Pneumonia

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in Wuhan, China, on 31 December 2019.1 The World Health Organisation (WHO) declared the outbreak a global health emergency on 30 January 2020, and there are more than 100,000 confirmed cases in 93 countries as of 7 March 2020.2 At this early stage of the outbreak, COVID-19 has already far exceeded the combined number of cases and deaths from Middle East Respiratory Syndrome-CoVirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS).3

On 23 January 2020, Singapore confirmed its first imported case of COVID-19, a tourist from Wuhan, China,4 and its first cluster of local transmission on 4 February 2020. As of 7 March 2020, there have been 130 cases of COVID-19 in Singapore, with approximately 15% developing respiratory failure requiring mechanical ventilation.5

In this report, we describe a patient with rapid clinical deterioration and the development of acute respiratory distress syndrome (ARDS). Unfortunately, while the cases of COVID-19 continue to escalate at an alarming rate worldwide, not much is known about the clinical features and risk factors for ARDS and critical illness, although...
recently published data suggests that advanced age and comorbidities such as cardiovascular disease may be associated with more severe disease. We aim to review our current understanding of critical illness from COVID-19 and explore areas where more research is urgently needed.

**Case Presentation**

A 64-year-old Chinese Singaporean man presented with a fall that was preceded by disziness. He also reported a 1-week history of fever and a 1-day history of dyspnoea. He had no significant past medical history. He worked as a taxi driver and reported ferrying passengers who were tourists from mainland China in the preceding weeks. He denied any recent travel history or contact with persons with COVID-19.

Clinically, he was alert and comfortable. His temperature was 39.0°C, oxygen saturation was 92% on room air and respiratory rate was 20 breaths/min. On examination, his lungs were clear to auscultation. Laboratory investigations revealed a haemoglobin concentration of 14.1 g/dL, white blood cell count of 4.6 × 10⁹/L, lymphopenia with a lymphocyte count of 0.23 × 10⁹/L (normal 1–3) and a platelet count of 147 × 10⁹/L. C-reactive protein was elevated at 87.9 mg/L (normal 0.2–9.1) and procalcitonin 0.55 µg/L (normal <0.50).

His renal function tests, liver function tests and serum lactate on admission were normal. Chest radiograph on admission showed subtle ground glass opacities in the lower zones with minor interstitial changes at the right base and atelectasis in the left lower zone. There was no consolidation or pleural effusion (Fig. 1A). In view of his contact history with Chinese tourists, the patient was immediately isolated in an airborne infection isolation room (AIIR). Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) performed on a throat swab specimen was positive for SARS-CoV-2, and patient was started on lopinavir/ritonavir (Kaletra) on day 2 of hospitalisation.

Over the next 2 days, oxygen saturation was stable on 3 L/min flow of oxygen, and other vital signs were normal apart from a respiratory rate of 18–20 breaths/min. However, on day 3 of hospitalisation (within 48 hours of presentation), he deteriorated rapidly with severe hypoxic respiratory failure requiring high flow oxygen supplementation via a face mask. A repeat chest radiograph showed rapid development of bilateral diffuse ground glass opacities (Fig. 1B). He was intubated and initiated on mechanical ventilation.

To minimise the risk of disease transmission to healthcare workers during intubation, a high efficiency particulate air (HEPA) mechanical filter was used with the bag-valve-mask interface, with an emphasis on adequate pre-oxygenation and rapid sequence induction to minimise dispersion of respiratory droplets. An arterial blood gas after initial stabilisation showed a \( \text{PaO}_2 \) of 80 mmHg.

![Fig. 1. A: Chest radiograph on admission showed minimal ground-glass opacities in the lower zones with interstitial thickening in the right base and atelectasis in the left lower zone. No consolidation or pleural effusion was evident. B: Repeat chest radiograph 2 days later showed rapid development of diffuse ground-glass opacities bilaterally. The patient was intubated on the same evening.](image-url)
while on FiO$_2$ 0.7 and positive end-expiratory pressure (PEEP) of 10 cmH$_2$O. There was significant ventilator dyssynchrony despite deep sedation and with the presence of moderate-severe ARDS (PaO$_2$/FiO$_2$ 114), a decision was made to initiate neuromuscular blockade to maintain lung protective ventilation.

Oxygenation improved during this period of paralysis and on day 2 of mechanical ventilation, he was supported with volume-controlled ventilation: tidal volume of 350 mL (5.0 mL/kg predicted body weight), FiO$_2$ 0.4, PEEP 10 cmH$_2$O, respiratory rate 30 breaths/min with a plateau pressure of 20 cmH$_2$O. A repeat arterial blood gas showed a pH of 7.31, PaCO$_2$ 51 mmHg and PaO$_2$ 78 mmHg. The patient did not require prone ventilation. Computed tomography (CT) scan of his thorax on day 8 of hospitalisation revealed diffuse ground glass opacities and consolidation in the dependent segments of both lungs (Fig. 2) consistent with ARDS. The patient was also started on empirical broad-spectrum antibiotics, but these were subsequently discontinued after 8 days when all bacterial cultures returned negative.

Despite the withholding of sedative and analgesia agents, the patient’s Glasgow Coma Scale (GCS) remained depressed and only fully recovered 4 days after all sedatives were discontinued. There were no obvious metabolic disturbances and CT brain was normal. However, on day 10, his ventilatory requirements increased along with increased purulent endotracheal tube (ETT) secretions and the development of new left midzone consolidation on chest radiograph (Fig. 3).Pseudomonas aeruginosa was isolated from ETT aspirates. He completed 7 days of culture-directed antibiotics for ventilator-associated pneumonia and was successfully extubated on day 14 (after 11 days of mechanical ventilation).

During his ICU stay, RT-PCR for SARS-CoV-2 (ETT and throat swab specimens) was performed every 2 days. The first negative SARS-CoV-2 RT-PCR was only achieved on day 15 of hospitalisation, approximately 3 weeks from the onset of symptoms. This was followed by resolution of lymphopenia 1 day later. Incidentally, the patient had diarrhoea on the first 2 days of hospitalisation, even before the initiation of lopinavir/ritonavir. SARS-CoV-2 was detected by RT-PCR on the stool samples; Clostridium difficile toxin assays yielded negative results. The events and progress of his ICU stay is illustrated in Figure 4.

Discussion

We describe the clinical course of a COVID-19 patient who rapidly developed ARDS requiring intubation. This

![Fig. 2](image-url) Axial images showed lung and soft tissue reconstruction and coronal image revealed lung reconstruction. Contrast-enhanced chest computed tomography showed ground-glass opacities predominantly in the upper lobes, with stark thin rim of subpleural sparing. Mild smooth intralobular septal thickening giving the appearance of “crazy paving” was observed. Consolidation was present in the dependent segments of both lungs with an asymmetric distribution, predominantly involving the right lower lobe. An incidental small thin-walled subpleural cyst in the right upper lobe likely represents a pneumatocele. Neither intrathoracic lymphadenopathy nor pleural effusion was observed.
Fig. 3. A: Chest radiograph after endotracheal intubation. B: Chest radiograph on day 4 showed mild improvement in extensive airspace opacification. C: Chest radiograph on day 11 showed interval development of patchy consolidation in right lung and focal consolidation in left mid-zone. A right internal jugular venous catheter was inserted. Endotracheal and nasogastric tubes are in-situ in both images.

case highlights the need to identify risk factors associated with critical illness so that patients at higher risk can be promptly identified and monitored closely. This case report also leads to a much needed discussion of what we currently understand about critical illness from COVID-19, while we face the threat of a worldwide pandemic.

Incidence of ARDS and Critical Illness

There is a wide range in the reported incidence of ARDS or critical illness from COVID-19. Initial studies from hospitals in Wuhan, China report an alarming incidence of ARDS (17 - 29%) and critical illness requiring ICU admission (23–32%) (Table 1). The incidence may even be underestimated, considering that in some studies the majority of patients remained hospitalised. Conversely, the reported incidence of critical illness in areas away from the epicentre of the disease outbreak appears to be lower. Guan et al published a study of 1,099 patients from 30 provinces in China and reported an incidence of 3–5% for ARDS or admission to ICU. In this study, the vast majority (94%) of patients remained hospitalised at the time of analysis, again suggesting that outcomes may be significantly underestimated and the study better described as a cross sectional survey of hospitalised patients. Differences in age and comorbidities (Table 1) may also account for these differences as well.

Additionally, patients involved in some of these studies may have milder disease. In Zhejiang province, all persons with respiratory symptoms or significant contact history were advised to go to hospitals, and ARDS was reported in only 1 of 62 hospitalised patients. Nevertheless, it is clear that the clinical spectrum of COVID-19 ranges widely from asymptomatic or mild illness to critical illness with a high risk of mortality. Large multicentre studies from other countries with adequate follow-up to hospital discharge or death will shed more light on the incidence of critical illness which is crucial for resource planning in healthcare systems all over the world.

Critical Illness from COVID-19: Clinical Features and Risk Factors

Of concern is the rapid clinical deterioration observed in our patient. Together with the threat of a worldwide pandemic and the wide spectrum of clinical severity observed with COVID-19, there is a need for early identification of patients at higher risk of critical illness. Unfortunately, the risk factors and clinical characteristics of ARDS from COVID-19 are still uncertain. What seems consistent, however, is that ARDS and critical illness appear to develop most commonly between 1–2 weeks after the onset of symptoms. Our patient developed ARDS at day 9 of symptoms, similar to published studies (Table 2).

Similar with MERS-CoV and SARS, patients with older age, presence of comorbidities (cardiovascular and cerebrovascular diseases), and dyspnoea appear to have worse outcomes. The reported median age of patients who required ICU admission was 63–66 years, compared to 46–51 years of age for non-ICU patients. Similar differences in age were also seen between survivors and non-survivors. While fever and cough was observed in most patients, dyspnoea was reported in about 30–50%, and based on studies from Wuhan, China, approximately half of patients with dyspnoea required admission to the ICU. Pre-existing chronic lung disease is also a concern. In the
Fig. 4. Timeline of clinical course of patient from day of hospitalisation. COVID-19: Coronavirus disease 2019; ETT: Endotracheal tube; PEEP: Positive end expiratory pressure
Table 1. Comparison of Outcomes in Patients with Coronavirus Disease (COVID-19) Infections

| Cohort          | Huang et al                      | Chen et al                      | Wang et al                      | Yang et al                      | Xu et al                      | Wu et al                      | Guan et al                      |
|-----------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Centre/s        | Jin Yin Tan Hospital, Wuhan, China | Jin Yin Tan Hospital, Wuhan, China | Zhongnan Hospital, Wuhan, China | Jin Yin Tan Hospital, Wuhan, China | 7 hospitals in Zhejiang, China | 3 hospitals in Jiangsu, China | 552 hospitals in 30 provinces, China |
| Period of hospitalisation/recruitment | 16 Dec 2019 – 2 Jan 2020 | 1 Jan – 20 Jan 2020 | 1 Jan – 28 Jan 2020 | 24 Dec 2019 – 12 Jan 2020 | 10 Jan – 26 Jan 2020 | 22 Jan – 14 Feb 2020 | 11 Dec 2019 – 29 Jan 2020 |
| Final follow-up date | 22 Jan 2020 | 25 Jan 2020 | 3 Feb 2020 | 9 Feb 2020 | 26 Jan 2020 | 14 Feb 2020 | 31 Jan 2020 |
| No. of patients  | 41 | 99 | 138 | 201 | 62 | 80 | 1099 |
| Age, years*     | 49 (41 – 58) | 56 (13) | 56 (42 – 68) | – | 41 (32 – 52) | 46 (31 – 62) | 47 (35 – 58) |
| Comorbidity     | Hypertension | 15% | – | 31% | – | 8% | – | 15% |
|                 | Diabetes Mellitus | 20% | – | 10% | – | 2% | – | 7% |
|                 | Cardiovascular disease | 15% | 40% | 15% | – | – | – | 3% |
|                 | Cerebrovascular disease | – | – | 5% | – | – | 2% | 1% |
|                 | Chronic respiratory disease | 2% | 1% | 3% | – | 2% | 1% | 1% |
| Outcomes        | Admission to ICU | 32% | 23% | 26% | 27% | 2% | 0% | 5% |
|                 | ARDS | 29% | 17% | 20% | 17% | 2% | 0% | 3% |
|                 | Death | 15% | 11% | 4% | 17% | 0% | 0% | 1% |
|                 | Remain hospitalised at time of analysis | 17% | 58% | 62% | 6% | 98% | 76% | 94% |

ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit
*Data expressed in median (interquartile range) or mean (standard deviation). Unfilled columns represent unavailable data.
Table 2. Comparison of Outcomes of Patients with Coronavirus Disease 2019 (COVID-19) Infection Who Required ICU Admission

| Cohort | Huang et al | Chen et al | Wang et al | Yang et al | Guan et al |
|--------|-------------|------------|------------|------------|------------|
| Centre/s | Jin Yin Tan Hospital, Wuhan, China | Jin Yin Tan Hospital, Wuhan, China | Zhongnan Hospital, Wuhan, China | Jin Yin Tan Hospital, Wuhan, China | 552 hospitals in 30 provinces, China |
| Period of hospitalisation/recruitment | 16 Dec 2019 – 2 Jan 2020 | 1 Jan – 20 Jan 2020 | 1 Jan – 28 Jan 2020 | 24 Dec 2019 – 12 Jan 2020 | 11 Dec 2019 – 29 Jan 2020 |
| Final follow-up date | 22 Jan 2020 | 25 Jan 2020 | 3 Feb 2020 | 9 Feb 2020 | 31 Jan 2020 |
| No. of patients | 13 | 23 | 36 | 52 | 67× |
| Age, years† | 49 (41 – 61) | – | 66 (57 – 78) | 60 (13) | 63 (53 – 71) |
| Comorbidity | | | | | |
| Hypertension | 15% | – | 58% | – | – |
| Diabetes Mellitus | 8% | – | 22% | 17% | 36% |
| Cardiovascular disease | 23% | – | 25% | – | 27% |
| Cerebrovascular disease | – | – | 17% | 14% | 6% |
| Chronic respiratory disease | 8% | – | 8% | 8% | 10% |
| Days from symptom onset to ARDS | 9 (8 – 14) | – | 8 (6 – 12) | – | – |
| Days from symptom onset to ICU admission | 11 (8 – 17) | – | 10 (6 – 12) | 10 (7 – 13) | – |
| Outcomes in ICU | | | | | |
| Nosocomial infection | 31% | – | – | 14% | – |
| Shock | 23% | 17% | 31% | 35% | 13% |
| Renal replacement therapy | 23% | 39% | 6% | 17% | 12% |
| ARDS | 85% | 74% | 75% | 67% | 40% |
| Mechanical ventilation | 15% | 17% | 47% | 71% | 37% |
| ECMO | 15% | 12% | 11% | 12% | 8% |
| Death | 38% | 48% | 17% | 62%‡ | 22% |
| Remains hospitalised at end of study | 8% | – | 58% | 23% | 76% |
| Remains on mechanical ventilation at end of study | – | – | 17% | 1% | – |

ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; ECMO: Extracorporeal membrane oxygenation

*Composite outcome of death, ICU admission or mechanical ventilation.
†Data is expressed as median (interquartile range) or mean (standard deviation). Unfilled columns represent unavailable data.
‡28-day ICU mortality.
study by Guan et al, more than half of patients with chronic obstructive pulmonary disease and COVID-19 infection were admitted to ICU or required mechanical ventilation.\textsuperscript{12}

Our patient’s age (64 years old) and presenting symptom of dyspnoea certainly constituted worrisome features. Additionally, there was significant lymphopenia on initial blood tests, which has been reported to be associated with critical illness.\textsuperscript{8,10,17} Neutrophilia, hypoalbuminemia, elevated levels of lactate dehydrogenase (LDH) and D-dimer were other identified markers of critical illness in COVID-19 that were seen in our patient.\textsuperscript{8,10,17} These observations seem to be consistent with SARS, where multivariate analysis identified elevated LDH and neutrophilia as markers associated with worse outcomes.\textsuperscript{16} However, these markers are non-specific and are commonly found in critically ill patients.

What will be useful to clinicians would be an early surrogate of disease severity, ideally before the onset of critical illness. Whether the degree of lymphopenia or LDH elevation can serve as early markers of disease severity or even a surrogate for disease recovery from COVID-19 is still unclear. In a study involving non-critically ill patients, Young et al reported a decline in viral loads (based on RT-PCR cycle thresholds) after reaching a peak soon after the onset of symptoms.\textsuperscript{18} A similar trend was observed in our patient. It remains to be seen if trends in the viral load can serve as a surrogate for disease recovery and more studies are needed in this area.

In our patient, CT chest showed extensive multilobar ground-glass changes with intralobular septal thickening and more confluent consolidation in the dependent portions of the lungs. Despite the peripheral location of the ground-glass changes, there were thin rims of subpleural sparing which—to our knowledge—has not been previously reported. Nevertheless, ground-glass opacities with or without consolidation—with posterior and peripheral predominance—appear to be the most common finding in COVID-19 pneumonia,\textsuperscript{19,20} as well as MERS-CoV and SARS.\textsuperscript{21,22} The lack of thoracic lymphadenopathy and pleural effusions in the patient is also consistent with reported findings with COVID-19.\textsuperscript{19,20}

Normal chest imaging, however, does rule out the development of severe illness. Guan et al reported that up to 23% and 12% of patients requiring ICU admission had a normal chest radiograph and CT imaging, respectively.\textsuperscript{12} Despite the rapid deterioration observed in our patient, only subtle ground-glass and interstitial changes are seen on the initial chest radiograph. A limitation of this observation is that it is based on a single case report. However, with more studies, we will hopefully be able to shed more light on the clinical course of patients who develop critical illness. Nevertheless, it will be prudent for clinicians to closely monitor patients with advanced age, comorbidities or dyspnoea, especially at 1–2 weeks from symptom onset.

Interestingly, our patient also remained in a semi-conscious state for almost 4 days despite withholding sedation and opioid therapy. No abnormalities were seen on CT brain, and no significant metabolic disturbances could explain the degree of unconsciousness. The patient regained full consciousness with no neurological deficit over the next few days. While septic encephalopathy is a likely diagnosis, a postulation was also the possible accumulation of fentanyl due to inhibition of cytochrome P450 by ritonavir, which is another important consideration for intensivists managing these patients.\textsuperscript{23}

Outcomes and Mortality of Critical Illness from COVID-19 Infection

While the estimated case fatality rate of 3.4% for COVID-19\textsuperscript{8} appears to be significantly lower than MERS-CoV (34.4%)\textsuperscript{9} and SARS (11%),\textsuperscript{24} critical illness from COVID-19 is associated with a high risk of mortality. Reported mortality rates of ICU patients in Jin Yin-Tan Hospital are between 38–62%, with more than 10% requiring extracorporeal membrane oxygenation (ECMO)\textsuperscript{8,10,11} Yang et al reported a 28-day mortality rate of 62% in patients who required ICU care; among patients who developed ARDS, 28-day mortality rate was reported to be 74%.\textsuperscript{11} The in-hospital mortality rate is likely to be even higher considering that at the time of analysis, the majority of survivors were still hospitalised, with 3 patients on mechanical ventilation, including 1 patient on ECMO.\textsuperscript{11} These reported mortality rates are indeed alarming, and even higher than mortality rates commonly seen in severe ARDS from other causes.\textsuperscript{25} It is possible that overwhelmed healthcare resources in Wuhan may affect quality of care, resulting in poorer outcomes.

In a recent publication by Xie et al, it was reported that there were severe shortages in ventilators and only about 25% of patients who died received invasive mechanical intubation.\textsuperscript{26} Additionally, the majority of patients were supported with high flow nasal cannula (HFNC) and non-invasive ventilation (NIV) and received systemic corticosteroids.\textsuperscript{8,11} It is unclear if delayed intubation or systemic corticosteroids may have adversely affected the outcomes of some patients.\textsuperscript{27} Importantly, as with our patient, up to a third of critically ill patients developed nosocomial or secondary bacterial infections, and intensivists managing these patients will need to remain vigilant as early administration of antibiotics may potentially improve outcomes.\textsuperscript{8,11} Finally, data is still lacking on the duration of mechanical ventilation or ECMO in survivors, both of which will be important for critical care management and resource planning.
Critical Illness from COVID-19: Clinical Management

In the absence of studies on COVID-19-induced ARDS, principles of management should be consistent with established guidelines for ARDS. WHO has also published similar guidelines for severe respiratory infections from COVID-19. We adopted lung protective ventilation, a conservative fluid strategy and neuromuscular blockade was initiated for moderate to severe ARDS with significant ventilator dyssynchrony despite sedation.

Due to a lack of clear benefit with HFNC and high failure rates with NIV in MERS-CoV infections, conventional oxygen therapy and early intubation were also principles of our management. The patient was started on lopinavir/ritonavir, with its presumed benefit largely extrapolated from experience with SARS. Remdesivir, a broad-spectrum pro-drug that inhibits RNA-dependent RNA-polymerase activity has shown promise in in vitro studies, and is currently being evaluated in a randomised, controlled clinical trial (NCT04257656).

To date, no anti-viral therapy has proven effective against COVID-19. Corticosteroids were not administered in this patient due to lack of evidence supporting its use and worse outcomes or delayed viral clearance observed in SARS and MERS-CoV patients. Finally, infection prevention and control will be a key component of ICU management, with an emphasis on healthcare workers to adopt appropriate personal protective equipment, practise standard contact and airborne precautions with eye protection, placement of known or suspected COVID-19 in AIIRs if available, and measures to minimise aerosolisation or dispersion of the patients’ respiratory droplets.

Interestingly, the patient also had diarrhoea with SARS-CoV-2 detected from stool samples. A small study by Young et al reported that of 8 patients who had stool samples collected, 4 had the virus detected by PCR in stool, suggesting that faecal-oral and contact transmissions may be a concern in patients with COVID-19 infection.

Conclusion

The clinical spectrum of COVID-19 appears to range widely from asymptomatic or mild illness to critical illness with a high risk of mortality. As patients can deteriorate rapidly, there is a need for more studies to identify early predictive markers for severe disease. Currently, the available evidence suggests that patients with dyspnoea, advanced age (≥60 years old) or coexisting comorbidities should be monitored closely, especially at 1–2 weeks after symptom onset. In the absence of a clear dysregulated host response to infection, laboratory abnormalities such as lymphopenia or elevated LDH may potentially serve as early surrogate markers for the development of critical illness.

While we await studies to shed more light on definitive treatment options, management principles of COVID-19-induced ARDS are mainly supportive and should not differ from the management of ARDS from other causes, apart from the need for strict adherence to established infection control measures. It remains to be seen if any definitive anti-viral therapy will emerge in the near future.

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