Original Article

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.

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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-Coronavirus (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

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recently published data suggests that advanced age and comorbidities such as cardiovascular disease may be associated with more severe disease.[6] 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 4.6×10^9/L, lymphopenia with a lymphocyte count of 0.23×10^9 per L (normal 1–3) and platelet count of 147×10^9 per 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 hypoxemic 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 PaO_2 of 80 mmHg

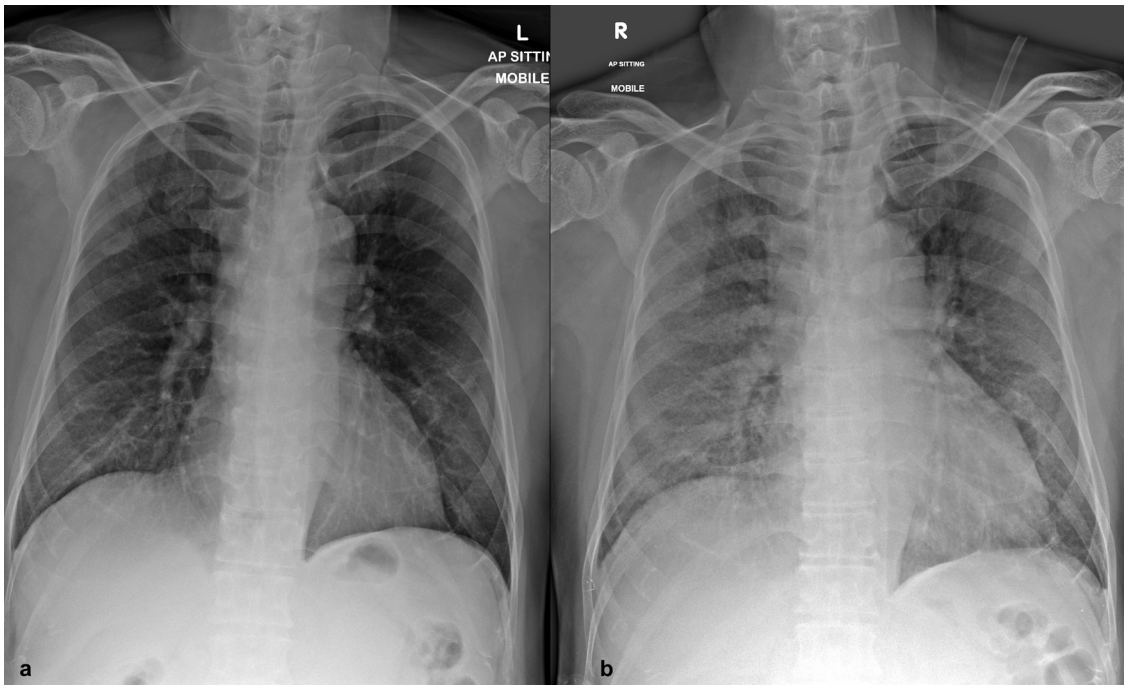

Fig. 1. A: Chest radiograph on admission showed minimal ground-glass opacities in the lower zones with interstitial thickening in the right base and atelectasis in the left lower zone. No consolidation or pleural effusion was evident. B: Repeat chest radiograph 2 days later showed rapid development of diffuse ground-glass opacities bilaterally. The patient was intubated on the same evening.

while on FiO_2 0.7 and positive end-expiratory pressure (PEEP) of 10 cmH_2O. There was significant ventilator dyssynchrony despite deep sedation and with the presence of moderate-severe ARDS (PaO_2/FiO_2 114),[7] 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_2O, respiratory rate 30 breaths/min with a plateau pressure of 20 cmH_2O. 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

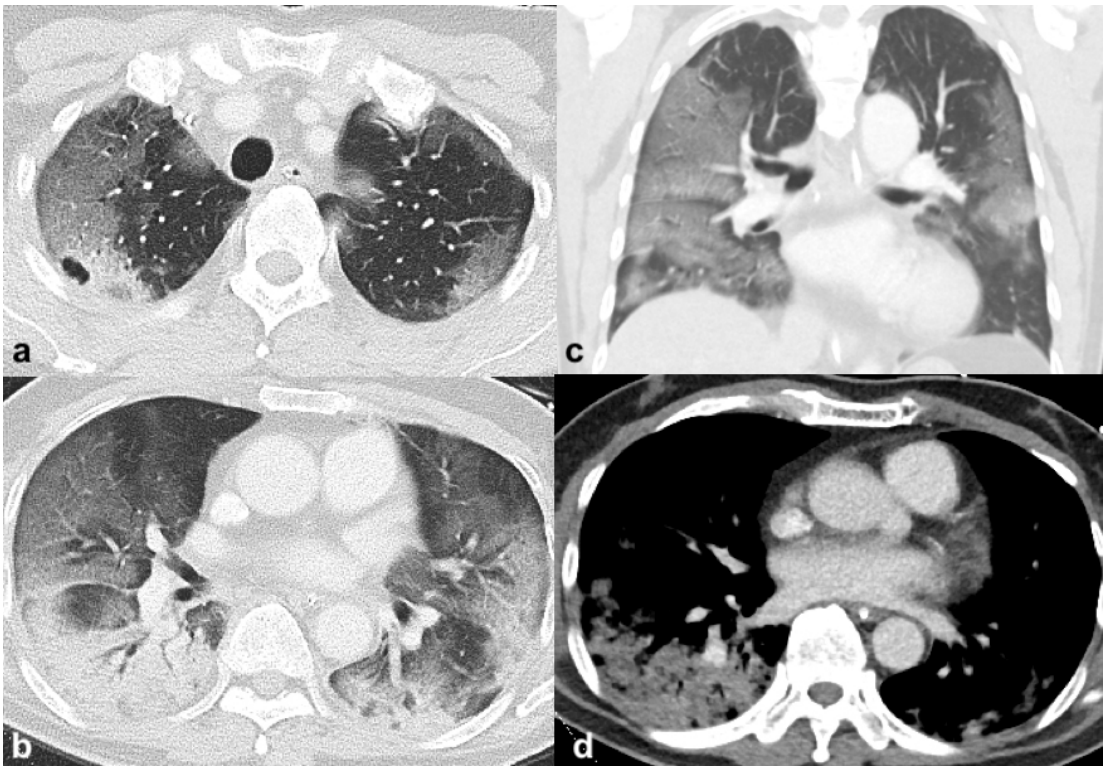

Fig. 2. Axial images showed lung and soft tissue reconstruction and coronal image revealed lung reconstruction. Contrast-enhanced chest computed tomography showed ground-glass opacities predominantly in the upper lobes, with stark thin rim of subpleural sparing. Mild smooth intralobular septal thickening 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.

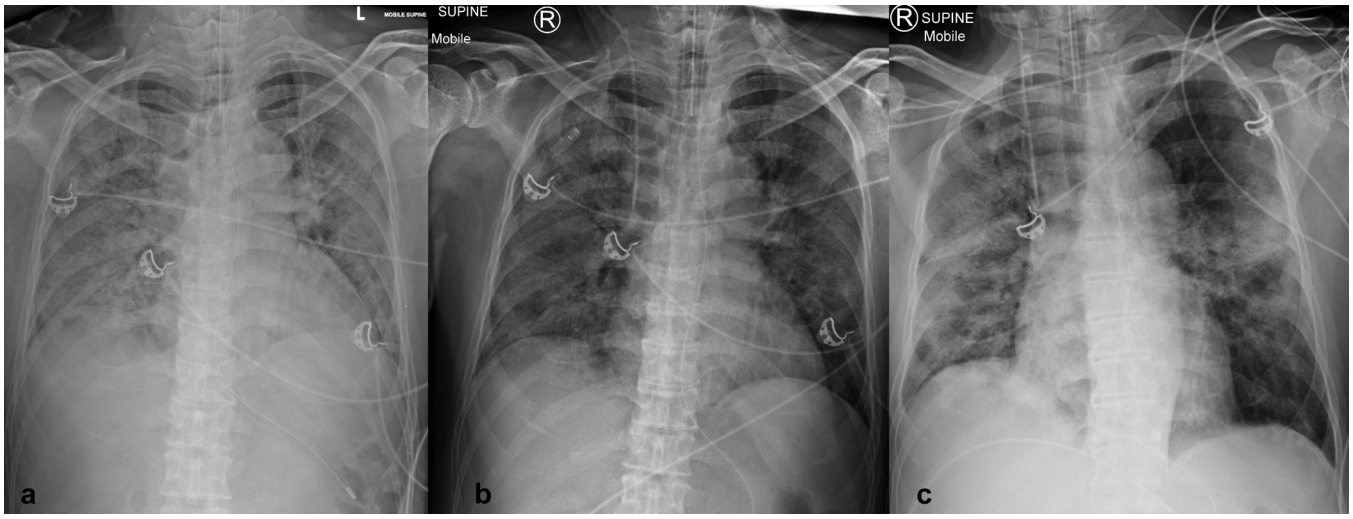

Fig. 3. A: Chest radiograph after endotracheal intubation. B: Chest radiograph on day 4 showed mild improvement in extensive airspace opacification. C: Chest radiograph on day 11 showed interval development of patchy consolidation in right lung and focal consolidation in left mid-zone. A right internal 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).[8-11] The incidence may even be underestimated, considering that in some studies the majority of patients remained hospitalised.[9,10] 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.[12] 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.[12] Differences in age and comorbidities (Table 1) may also account for these differences as well.[13,14]

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.[13] 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.[6] 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.[8,10,11] Our patient developed ARDS at day 9 of symptoms, similar to published studies (Table 2).[8,10]

Similar with MERS-CoV[15] and SARS[16], patients with older age, presence of comorbidities (cardiovascular and cerebrovascular diseases), and dyspnoea appear to have worse outcomes.[8,10,11] 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.[10,12] Similar differences in age were also seen between survivors and non-survivors.[8,17] 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.[8,10] Pre-existing chronic lung disease is also a concern. In the

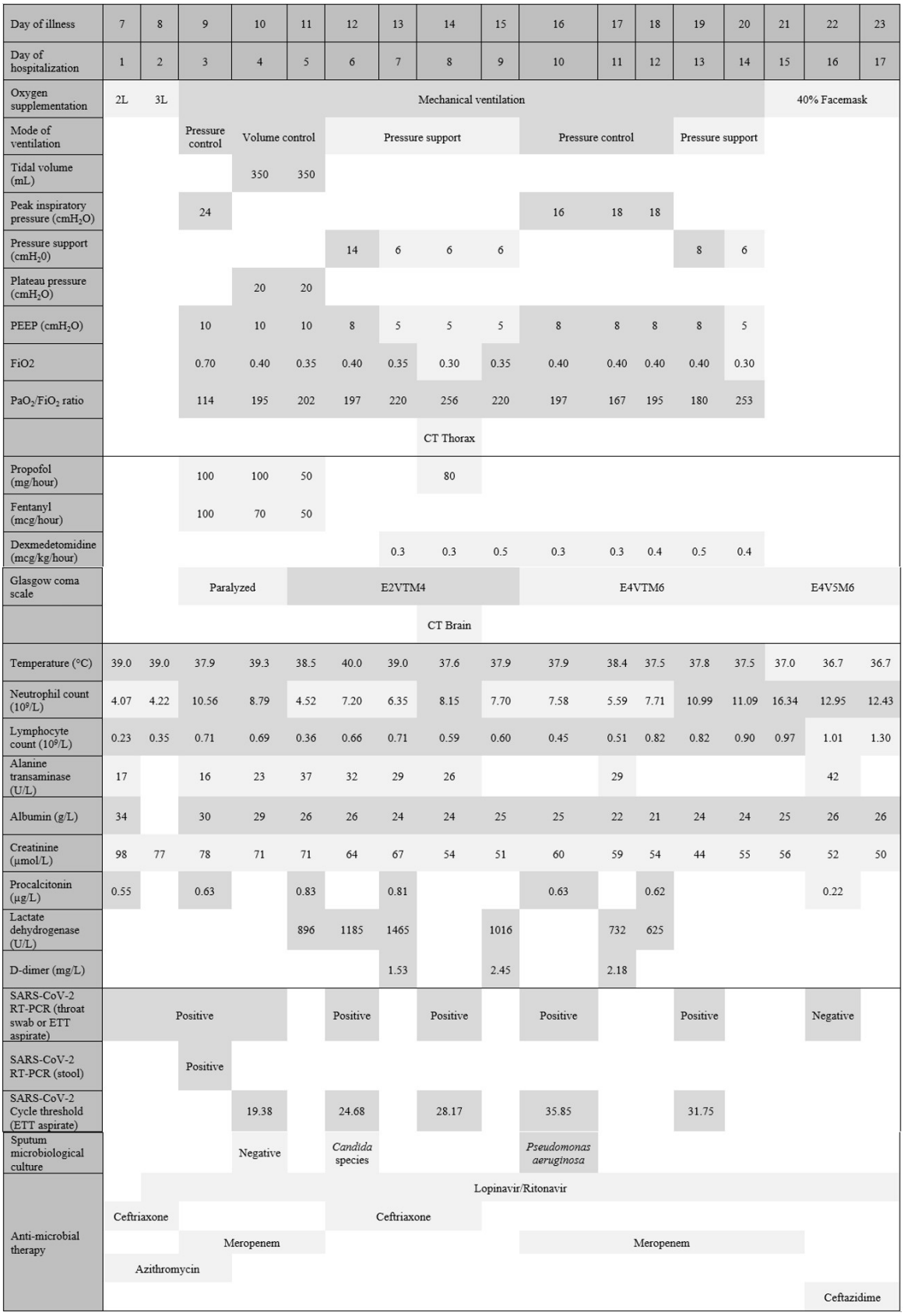

Fig. 4. Timeline of clinical course of patient from day of hospitalisation. COVID-19: Coronavirus disease 2019; ETT: Endotracheal tube; PEEP: Positive end expiratory pressure

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.[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.[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.[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.[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.[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,[19,20] as well as MERS-CoV and SARS.[21,22] The lack of thoracic lymphadenopathy and pleural effusions in the patient is also consistent with reported findings with COVID-19.[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.[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.[23]

Outcomes and Mortality of Critical Illness from COVID-19 Infection

While the estimated case fatality rate of 3.4% for COVID-19[2] appears to be significantly lower than MERS-CoV (34.4%)[3] and SARS (11%),[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).[8,9,11] 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%.[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.[11] These reported mortality rates are indeed alarming, and even higher than mortality rates commonly seen in severe ARDS from other causes.[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.[26] Additionally, the majority of patients were supported with high flow nasal cannula (HFNC) and non-invasive ventilation (NIV) and received systemic corticosteroids.[8,11] It is unclear if delayed intubation or systemic corticosteroids may have adversely affected the outcomes of some patients.[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.[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.[28] 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,[29] 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.[30,31] Remdesivir, a broad-spectrum pro-drug that inhibits RNA-dependant RNA-polymerase activity has shown promise in in vitro studies, and is currently being evaluated in a randomised, controlled clinical trial (NCT04257656).[32]

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[33] and worse outcomes or delayed viral clearance observed in SARS and MERS-CoV patients.[34,35] Finally, infection prevention and control will be a key component of ICU management,[36] 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.[37]

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,[18] suggesting that faecal-oral and contact transmissions may be a concern in patients with COVID-19 infection.[38]

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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REFERENCES

1. Wuhan Municipal Health Commission. Report of clustering pneumonia of unknown etiology in Wuhan City. Available at: http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989. Accessed on 24 February 2020.
2. World Health Organisation. Coronavirus disease 2019 (COVID-19), Situation report 47. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200307-sitrep-47-covid-19.pdf. Accessed on 1 March 2020.
3. Park M, Thwaites RS, Openshaw PJM et al. COVID-19: Lessons from SARS and MERS. Eur J Immunol [Epub on 27 February 2020]. DOI:10.1002/eji.202070035.
4. Wong JEL, Leo YS, Tan CC. COVID-19 in Singapore—Current experience critical global issues that require attention and action. JAMA [Epub on 20 February 2020]. DOI:10.1001/jama.2020.2467.
5. Ministry of Health, Singapore. Updates on COVID-19 (Coronavirus disease 2019) local situation, 2020. Available at: https://www.moh.gov.sg/covid-19. Accessed on 10 March 2020.
6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA [Epub on 24 February 2020]. DOI:10.1001/jama.2020.2648.
7. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1572–82.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
9. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalised patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA [Epub on 7 February 2020]. DOI:10.1001/jama.2020.1585.
11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med [Epub on 24 February 2020]. DOI:10.1016/S2213-2600(20)30079-5.

12. Guan WJ, Ni ZY, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med [Epub on 28 February 2020]. DOI:10.1056/NEJMoa2002032.
13. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ [Epub on 19 February 2020]. DOI:10.1136/bmj.m606.
14. Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical characteristics of imported cases of COVID-19 in Jiangsu province: a multicenter descriptive study. Clin Infect Dis [Epub on 29 February 2020]. DOI:10.1093/cid/ciaa199.
15. Ahmed AE. The predictors of 3- and 30-day mortality in 660 MERS-CoV patients. BMC Infect Dis 2017;17:615.
16. Leong HN, Earnest A, Lim HH, Chin CF, Tan CSH, Puhaindran E, et al. SARS in Singapore— predictors of disease severity. Ann Acad Med Singapore 2006;35:326–31.
17. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med [Epub on 3 March 2020]. DOI:10.1007/s00134-020-05991-x.
18. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiological features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA [Epub on 3 March 2020]. DOI:10.1001/jama.2020.3204.
19. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging coronavirus 2019-nCoV pneumonia. Radiology [Epub on 6 February 2020]. DOI:10.1148/radiol.2020200274.
20. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology [Epub on 4 February 2020]. DOI:10.1148/radiol.2020200230.
21. Das KM, Lee EY, Langer RD, Larsson SG. Middle East respiratory syndrome coronavirus: what does a radiologist need to know? AJR Am J Roentgenol 2016;206:1193–201.
22. Ooi GC, Ma D. SARS: radiological features. Respirology 2003;8:S15–19.
23. Bruce RD, Moody DE, Altice FL, Gourevitch MN, Friedland GH. A review of pharmacological interactions between HIV or hepatitis C virus medications and opioid agonist therapy: implications and management for clinical practice. Expert Rev Clin Pharmacol 2013;6:249–69.
24. World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome. Available at: https://apps.who.int/iris/handle/10665/70863. Accessed on 1 March 2020.
25. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788–800.
26. Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky A. Critical care crisis and some recommedations during the COVID-19 epidemic in China. Intensive Care Med [Epub on 2 March 2020]. DOI:10.1007/s00134-020-05979-7.
27. Kang BJ, Koh YS, Lim CM, Huh JW, Baek SH, Han MJ, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015;41:623–32.
28. World Health Organisation. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. Available at: https://www.who.int/internal-publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed on 20 February 2020.
29. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160:389–97.
30. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax 2004;59:252–6.
31. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MML, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399–406.
32. Wang M, Cao R, Zhang L, Yang X, Liu X, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res [Epub on on 4 February 2020]. DOI:10.1038/s41422-020-0282-0.
33. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473–5.
34. Auyeung TW, Lee JSW, Lai WK, Choi CH, Lee HK, Lee JS, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005;51:98–102.
35. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med 2018;197:757–67.
36. Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for patients with confirmed coronavirus disease 2019 (COVID-19) or persons under investigation for COVID-19 in healthcare settings. Available at: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html. Accessed on 1 March 2020.
37. Tai DYH. SARS: how to manage future outbreaks? Ann Acad Med Singapore 2006;35:368–73.
38. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect 2020;9:386–9.