Original Article

Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from Coronavirus Disease 2019 (COVID-19) Infection

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Abstract

The outbreak of coronavirus disease 2019 (COVID-19) in December 2019 in the city of Wuhan in Mainland China has spread across the globe with >100,000 infected individuals and 3000 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 infection ranges from mild illness to ARDS with high mortality risk, there is need for research that identifies early markers of disease severity. Current evidence suggests that patients with advanced age, dyspnoea or pre-existing comorbidities should be monitored closely, especially at 1–2 weeks after symptom onset. It remains to be seen whether laboratory findings such as lymphopaenia or elevated lactate dehydrogenase may serve as early surrogates for critical illness or markers of disease recovery. Management of ARDS in COVID-19 patients 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 infection which are important for critical care management of patients and resource planning.

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Key words: Intensive Care, Mortality, Pneumonia, Risk factors

Introduction

The outbreak of coronavirus disease 2019 (COVID-19)—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—was first reported on 31 December 2019 in the city of Wuhan in Mainland China.[1] On 30 January 2020, the World Health Organization (WHO) declared the outbreak a global health emergency; as of 7 March 2020, >100,000 individuals in 93 countries had been infected by the virus.[2] At this early stage of the outbreak, COVID-19 has already exceeded the total 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 reported her first case of COVID-19 infection in a tourist from Wuhan.[4] On 4 February 2020, the country reported the first cluster of local transmission. By 7 March 2020, there were 130 COVID-19 cases and approximately 15% of them developed respiratory failure that required mechanical ventilation.[5]

In this report, we describe a patient who developed acute respiratory distress syndrome (ARDS) with rapid clinical deterioration. Unfortunately, not much is known

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about the clinical features and risk factors for ARDS and critical illness even as the number of COVID-19 cases continues to climb at an alarming rate throughout the world. However, recent published data suggested that advanced age and comorbidities such as cardiovascular disease may be associated with more severe disease.[6] In this review, we examine current understanding of critical illness from COVID-19 infection and explore areas where research is urgently needed.

Case Presentation

A 64-year-old Chinese man presented with a fall that was preceded by dizziness. He reported dyspnoea and fever that lasted 1 day and 1 week, respectively, and had no significant past medical history. Prior to presentation, he worked as a taxi driver and reported ferrying passengers who were tourists from Mainland China. He denied a history of recent travel or contact with individuals infected by 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 haemoglobin 14.1 g/dL, white blood cell count 4.6 × 10^9/L, lymphopaenia with lymphocyte count 0.23 × 10^9/L (normal 1–3 × 10^9/L) and platelet count 147 × 10^9/L. C-reactive protein was elevated at 87.9 mg/L (normal 0.2–9.1 mg/L) and procalcitonin was 0.55 µg/L (normal <0.50 µg/L).

On admission, findings of liver and renal function tests and serum lactate were normal, but chest radiograph showed subtle ground-glass opacities in lower zones with minor interstitial changes at the right base and atelectasis in left lower zone. Consolidation or pleural effusion was absent (Fig. 1A). In view of his recent contact with tourists from Mainland China, he was immediately isolated in an airborne infection isolation room (AIIR). Throat swab on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tested positive for SARS-CoV-2 and he was started on lopinavir/ritonavir (Kaletra) on day 2 of admission. Oxygen saturation was stable on 3 L/min flow of oxygen. Apart from a respiratory rate of 18–20 breaths/min, all vital signs were normal.

Within 48 hours of presentation, however, he deteriorated rapidly with severe hypoxemic respiratory failure that required high-flow oxygen supplementation with a face mask. Repeat chest radiograph showed rapid development of bilateral diffuse ground-glass opacities (Fig. 1B) and he was intubated and initiated on mechanical ventilation.

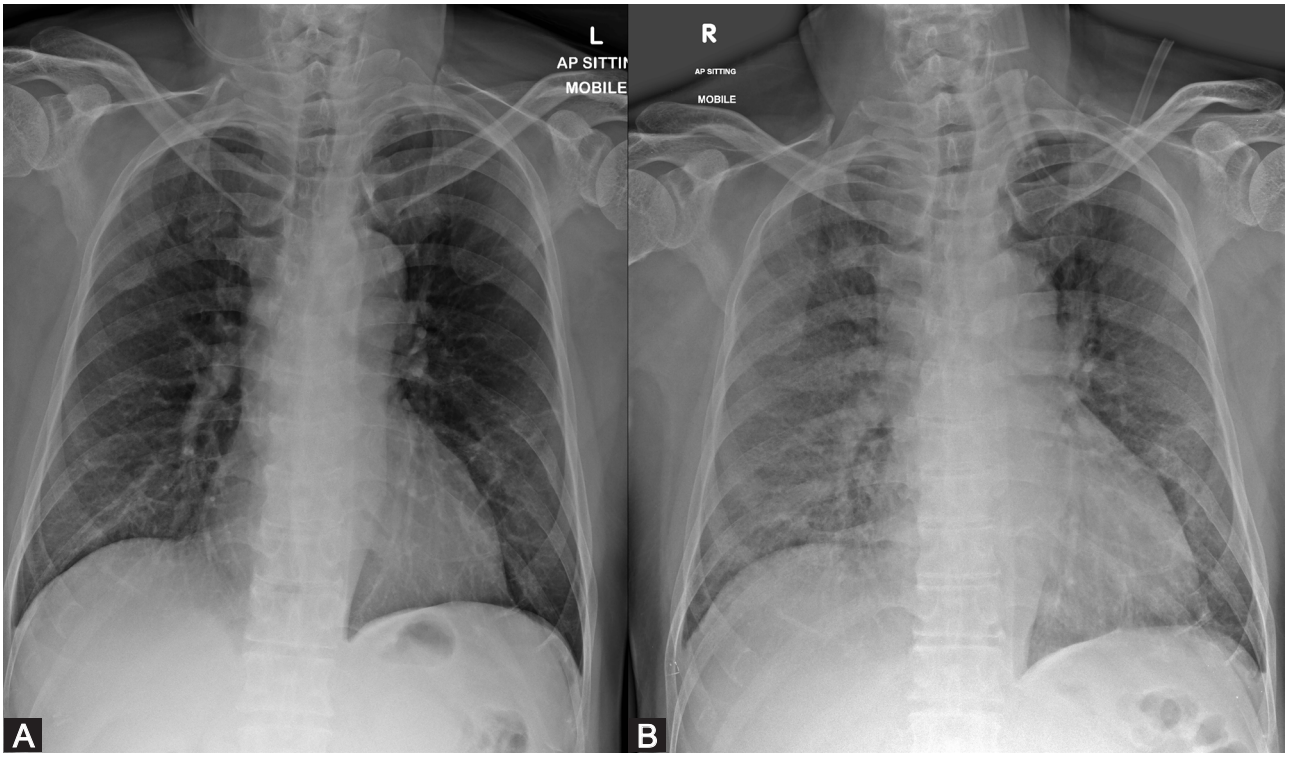


Fig. 1. A: On admission, chest radiograph showed minimal ground-glass opacities in lower zones with interstitial thickening in right base and atelectasis in left lower zone. No consolidation or pleural effusion was evident. B: On day 2, repeat chest radiograph showed rapid development of diffuse ground-glass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

To minimise risk of viral transmission to health workers during intubation, a high-efficiency particulate air mechanical filter was used with bag-valve-mask interface and an emphasis on adequate preoxygenation and rapid sequence induction to minimise dispersion of respiratory droplets. After initial stabilisation, arterial blood gas showed partial pressure of oxygen (PaO_2) of 80 mmHg, fraction of inspired oxygen (FiO_2) of 0.7 and positive end-expiratory pressure (PEEP) of 10 cmH_2O that were consistent with moderate to severe ARDS (PaO_2/FiO_2 114).[7] Despite deep sedation, significant ventilator dyssynchrony was observed, and neuromuscular blockade was initiated to maintain lung protective ventilation.

During this period of paralysis, oxygenation improved. On day 2 of mechanical ventilation, he was supported with volume-controlled ventilation: tidal volume 350 mL (5.0 mL/kg predicted body weight), FiO_2 0.4, PEEP 10 cmH_2O and respiratory rate 30 breaths/min with a plateau pressure of 20 cmH_2O. Repeat arterial blood gas showed pH 7.31, partial pressure of carbon dioxide 51 mmHg and PaO_2 78 mmHg. He did not require prone ventilation.

On day 8, computed tomography (CT) of thorax revealed diffuse ground-glass opacities and consolidation in the dependent segments of both lungs (Fig. 2), findings that were consistent with ARDS. He was started on

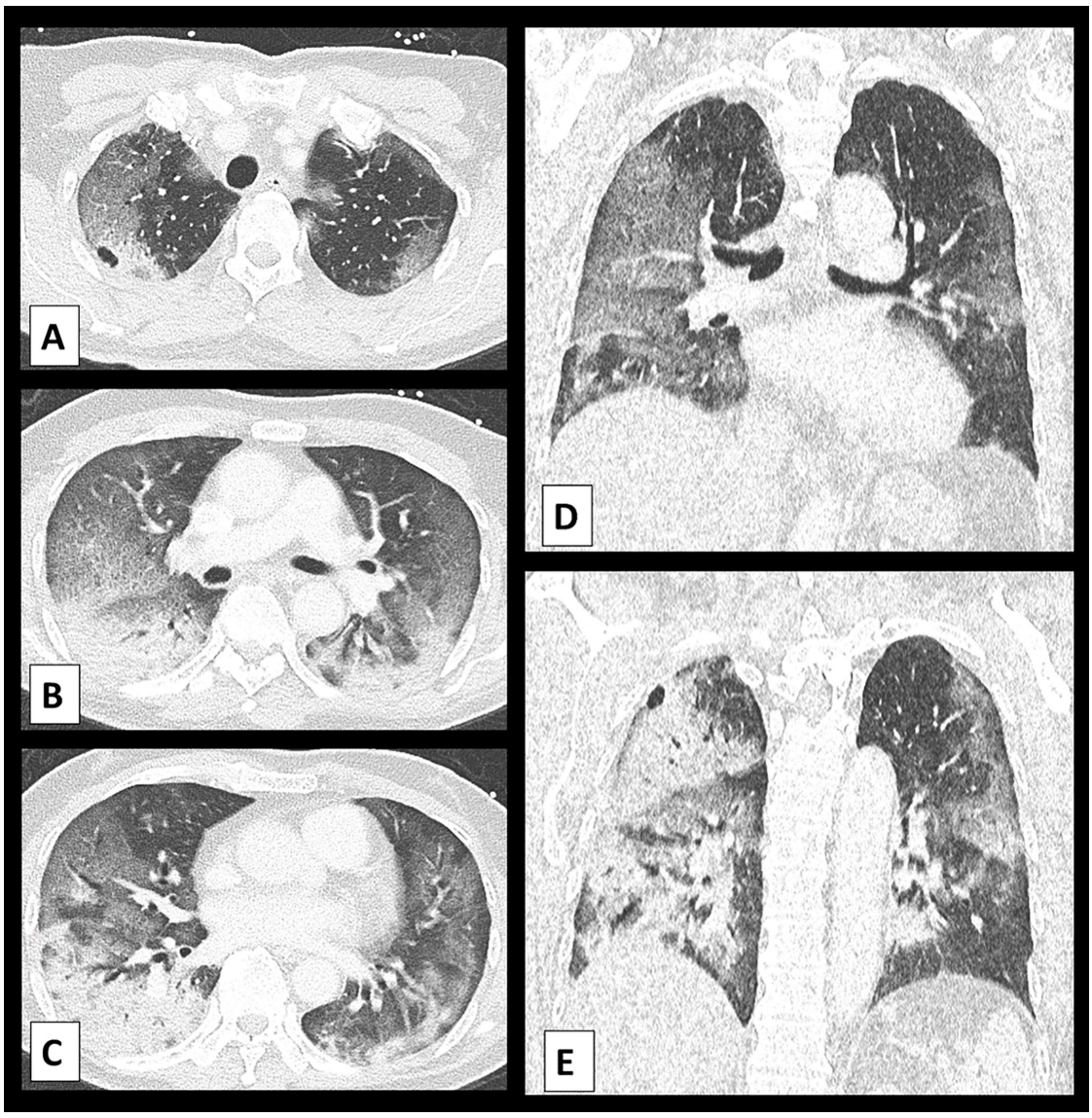


Fig. 2. Computed tomography (CT) of lung. A: Axial contrast-enhanced CT image showed ground-glass opacities that predominate in upper lobes with stark thin rim of subpleural sparing. B: Axial CT image showed mild, smooth intralobular septal thickening that gave the appearance of "crazy paving". C: Axial CT image showed consolidation in dependent segments of both lungs with an asymmetric distribution that involved predominantly the right lower lobe. D and E: Coronal CT images showed an incidental small, thin-walled subpleural cyst in right upper lobe that likely represents a pneumatocele. Neither intrathoracic lymphadenopathy nor pleural effusion was observed.

empirical broad-spectrum antibiotics, but these were discontinued after 8 days when all bacterial cultures returned negative. Despite withholding of sedative and analgesia agents, Glasgow Coma Scale remained depressed and full recovery was seen only after all sedatives were discontinued 4 days later. No metabolic disturbances were observed and brain CT was normal.

On day 10, his ventilatory requirements increased with a concurrent rise in purulent endotracheal tube (ETT) secretions and development of new left mid-zone 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. After 11 days of mechanical ventilation, he was successfully extubated on day 14.

During his stay in the Intensive Care Unit (ICU), RT-PCR for SARS-CoV-2 was performed on ETT and throat swab specimens on alternate days until the first negative culture was obtained on day 15 of admission, which was approximately 3 weeks after symptom onset. A day later, lymphopaenia resolved. Incidentally, he had diarrhoea during the first 2 days of admission before lopinavir/ritonavir was initiated and SARS-CoV-2 was detected in stool samples on RT-PCR; results of *Clostridium difficile* toxin assays were negative. The events and progress of his ICU stay are illustrated in Figure 4.

Discussion

In our patient, we described the clinical course of COVID-19 infection that developed rapidly into ARDS requiring intubation. This case highlighted the need to identify risk factors associated with critical illness so that at-risk patients can be promptly identified and closely monitored. It also prompts a discussion of our current understanding of critical illness from COVID-19 infection after the outbreak was declared a global pandemic by the WHO on 11 March 2020.[8]

Incidence of ARDS and Critical Illness

There is wide variability in the reported incidence of ARDS or critical illness from COVID-19 infection. As shown in Table 1, initial studies from hospitals in Wuhan city in Mainland China had reported an alarming incidence of ARDS (17–29%) and critical illness that required ICU admission (23–32%).[9-12] The reported incidence may be underestimated since most patients remained hospitalised in some of the studies.[10,11] Conversely, the reported incidence of critical illness in areas further away from the epicentre of the outbreak in Wuhan city appeared to be lower.

In their study of 1099 patients from 30 provinces in Mainland China, Guan et al reported an incidence of 3–5% for ARDS or admission to ICU.[13] In their study, most patients (94%) remained hospitalised at the time of writing, again suggesting that outcomes may be significantly underestimated. Consequently, their study is better described as a cross-sectional survey of hospitalised patients.[13] Differences in age and comorbidities may also account for these differences (Table 1).[14,15]

The true incidence of critical illness is difficult to determine due to differences in resources available for diagnostic testing, contact tracing and surveillance. In Zhejiang Province, individuals with respiratory symptoms or significant contact history with COVID-19

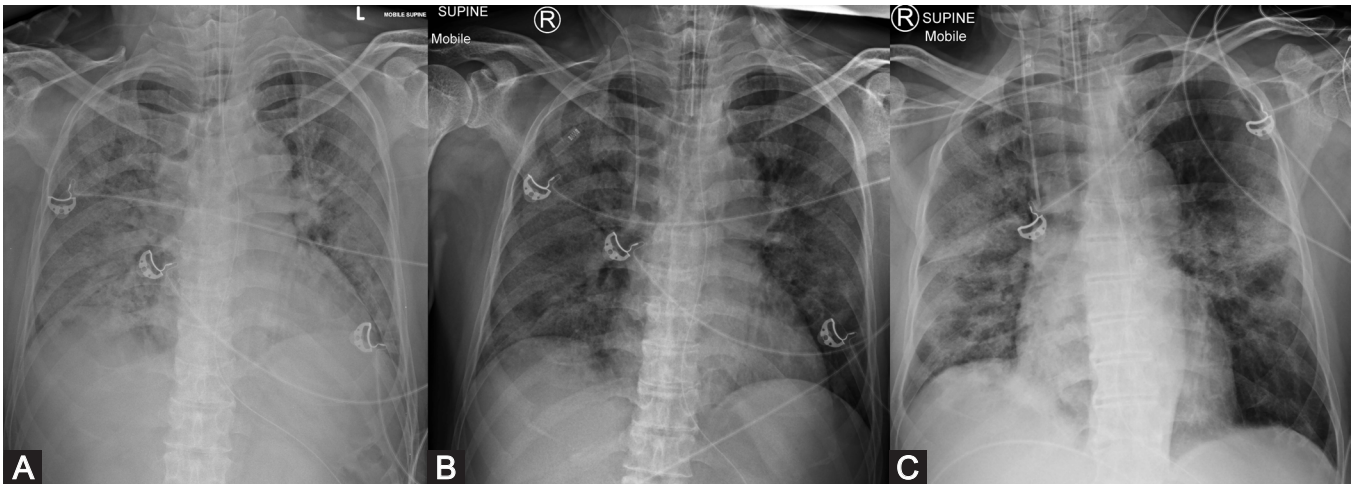
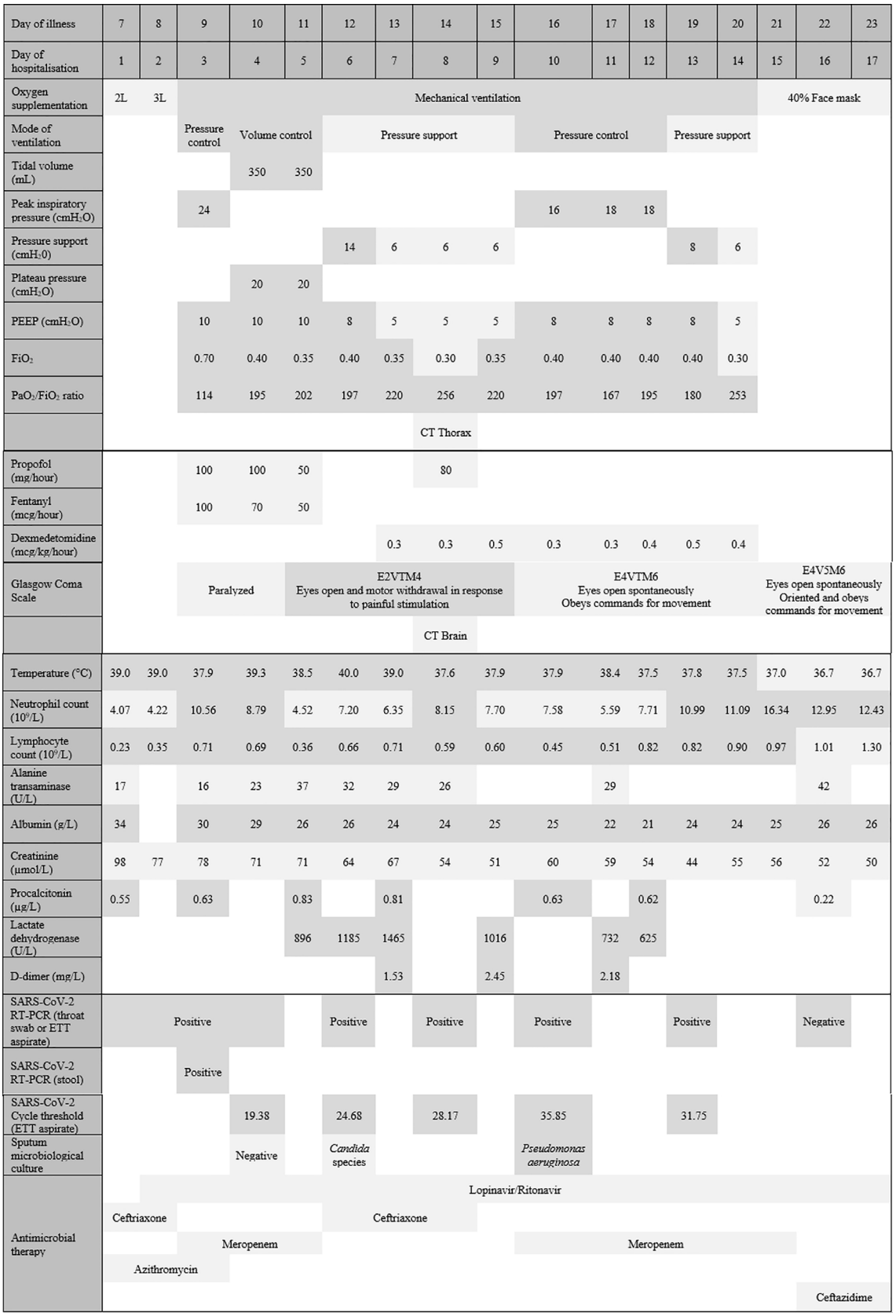


Fig. 3. A: Chest radiograph after endotracheal intubation. B: On day 4, chest radiograph showed mild improvement in extensive airspace opacification. C: On day 11, chest radiograph showed interval development of patchy consolidation in right lung and focal consolidation in left mid-zone. A nasogastric tube (A, B and C) and right internal jugular venous catheter (B and C) were inserted.



Day of illness	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Day of hospitalisation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Oxygen supplementation	2L	3L	Mechanical ventilation												40% Face mask		
Mode of ventilation			Pressure control	Volume control		Pressure support				Pressure control			Pressure support				
Tidal volume (mL)				350	350												
Peak inspiratory pressure (cmH_2O)			24							16	18	18					
Pressure support (cmH_20)						14	6	6	6				8	6			
Plateau pressure (cmH_2O)				20	20												
PEEP (cmH_2O)			10	10	10	8	5	5	5	8	8	8	8	5			
FiO_2			0.70	0.40	0.35	0.40	0.35	0.30	0.35	0.40	0.40	0.40	0.40	0.30			
PaO_2/FiO_2 ratio			114	195	202	197	220	256	220	197	167	195	180	253			
								CT Thorax									
Propofol (mg/hour)			100	100	50			80									
Fentanyl (mcg/hour)			100	70	50												
Dexmedetomidine (mcg/kg/hour)							0.3	0.3	0.5	0.3	0.3	0.4	0.5	0.4			
Glasgow Coma Scale			Paralyzed		E2VTM4 Eyes open and motor withdrawal in response to painful stimulation					E4VTM6 Eyes open spontaneously Obeys commands for movement					E4V5M6 Eyes open spontaneously Oriented and obeys commands for movement		
								CT Brain									
Temperature (°C)	39.0	39.0	37.9	39.3	38.5	40.0	39.0	37.6	37.9	37.9	38.4	37.5	37.8	37.5	37.0	36.7	36.7
Neutrophil count (10^9/L)	4.07	4.22	10.56	8.79	4.52	7.20	6.35	8.15	7.70	7.58	5.59	7.71	10.99	11.09	16.34	12.95	12.43
Lymphocyte count (10^9/L)	0.23	0.35	0.71	0.69	0.36	0.66	0.71	0.59	0.60	0.45	0.51	0.82	0.82	0.90	0.97	1.01	1.30
Alanine transaminase (U/L)	17		16	23	37	32	29	26			29					42	
Albumin (g/L)	34		30	29	26	26	24	24	25	25	22	21	24	24	25	26	26
Creatinine (μmol/L)	98	77	78	71	71	64	67	54	51	60	59	54	44	55	56	52	50
Procalcitonin (μg/L)	0.55		0.63		0.83		0.81			0.63		0.62				0.22	
Lactate dehydrogenase (U/L)					896	1185	1465		1016		732	625					
D-dimer (mg/L)							1.53		2.45		2.18						
SARS-CoV-2 RT-PCR (throat swab or ETT aspirate)	Positive					Positive		Positive		Positive			Positive			Negative	
SARS-CoV-2 RT-PCR (stool)			Positive														
SARS-CoV-2 Cycle threshold (ETT aspirate)				19.38		24.68		28.17		35.85			31.75				
Sputum microbiological culture				Negative		*Candida* species				*Pseudomonas aeruginosa*							
Antimicrobial therapy	Lopinavir/Ritonavir																
	Ceftriaxone					Ceftriaxone											
			Meropenem							Meropenem							
	Azithromycin																
																Ceftazidime	

Fig. 4. Clinical course of patient on admission. COVID-19: Coronavirus disease 2019; CT: Computed tomography; ETT: Endotracheal tube; FiO_2: Fraction of inspired oxygen; PaO_2: Partial pressure of oxygen; PEEP: Positive end-expiratory pressure; RT-PCR: Reverse transcriptase-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Table 1. Patient Outcomes from Coronavirus Disease 2019 Infection in Mainland China

Variable	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 in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Zhongnan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	7 hospitals in Zhejiang Province	3 hospitals in Jiangsu Province	552 hospitals in 30 provinces
Hospitalisation/recruitment	16 Dec 2019 – 2 Jan 2020	1 – 20 Jan 2020	1 – 28 Jan 2020	24 Dec 2019 – 12 Jan 2020	10 – 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
Number of patients	41	99	138	201	62	80	1099
Median age in years (IQR)	49 (41 – 58)	56 (13)	56 (42 – 68)	NA	41 (32 – 52)	46 (31 – 62)	47 (35 – 58)
Comorbidity (%)							
Hypertension	15	NA	31	NA	8	NA	15
Diabetes mellitus	20	NA	10	NA	2	NA	7
Cardiovascular disease	15	40	15	NA	NA	NA	3
Cerebrovascular disease	NA	NA	5	NA	2	NA	1
Chronic respiratory disease	2	1	3	NA	2	1	1
Outcome (%)							
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
Hospitalised at time of writing	17	58	62	6	98	76	94

ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; IQR: Interquartile range; NA: Not available

*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.

†Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, 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.

‡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 2020;DOI:10.1001/jama.2020.1585.

§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 2020;DOI:10.1016/S2213-2600(20)30079-5.

‖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 2020;DOI:10.1136/bmj.m606.

¶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 2020;DOI:10.1093/cid/ciaa199.

#Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;DOI:10.1056/NEJMoa2002032.

patients were advised to visit hospitals and ARDS was only reported in 1 out of 62 hospitalised patients.[14] Nevertheless, it is clear that the clinical spectrum of COVID-19 infection ranges widely from asymptomatic individuals to those with a mild form of the illness to patients with critical illness and with high mortality risk.[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 that is crucial to resource planning of health services from around the world.

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

In our patient, the observation of rapid clinical deterioration is concerning. With the wide spectrum of clinical severity observed in COVID-19 patients, it is necessary to identify patients who are at higher risk of critical illness. Unfortunately, the risk factors and clinical characteristics of ARDS from COVID-19 infection are still not fully known or understood. What appears to be a consistent finding, however, is that ARDS and critical illness mostly develop between 1–2 weeks after symptom onset.[9,11,12] Similar to findings from published studies (Table 2), our patient developed ARDS on day 9 after symptom onset.[9,11]

Like MERS-CoV[16] and SARS[17], patients with older age, comorbidities (such as cardiovascular and cerebrovascular diseases) and dyspnoea appeared to have worse outcomes.[9,11,12] Median age of ICU patients was 63–6 years compared to 46–51 years in non-ICU patients.[11,13] A similar finding for age was also seen between survivors and non-survivors.[9,18] While cough and fever were observed in most patients, dyspnoea was reported in about 30–50% of patients; based on studies from Wuhan city in Mainland China, approximately half of patients with dyspnoea required ICU admission.[9,11] Pre-existing chronic lung disease is also a concern. In the 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.[11]

The age of our patient (64 years old) and presence of dyspnoea were worrisome features. Additionally, initial blood tests revealed significant lymphopaenia which has been reported to be associated with critical illness.[9,11,18] Neutrophilia, hypoalbuminaemia and elevated levels of lactate dehydrogenase (LDH) and D-dimer were other markers of critical illness in COVID-19 infection that were seen in our patient.[9,11,18] These observations appear to be consistent with SARS, where multivariate analysis had identified elevated LDH and neutrophilia as markers that were associated with worse outcomes.[17] However, these markers are non-specific and are commonly found in critically ill patients.

For clinicians, an early surrogate of disease severity—ideally before the onset of critical illness—is useful. The issue of whether the degree of lymphopaenia or LDH elevation can be early markers of disease severity—or even a surrogate for disease recovery from COVID-19 infection—is still unclear. In their study of patients who were not critically ill, Young et al reported a decline in viral loads—based on RT-PCR cycle thresholds—after a peak was reached shortly after symptom onset.[19] This finding was also observed in our patient. However, it remains to be seen whether trends in viral loads can serve as a surrogate for disease recovery.

In our patient, chest CT 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 the best of our knowledge—have not been reported previously. Nevertheless, ground-glass opacities with or without consolidation—with posterior and peripheral predominance—appear to be the most common finding in COVID-19 pneumonia,[20,21] MERS-CoV and SARS.[22,23] In our patient, lack of thoracic lymphadenopathy and pleural effusions are also consistent with reported findings of COVID-19 infection.[20,21]

Findings of normal chest images, however, do not rule out the development of severe illness. Guan et al reported that up to 23% and 12% of patients who required ICU admission had normal chest radiographs and CT images, respectively.[13] Despite the rapid deterioration observed in our patient, only subtle ground-glass and interstitial changes were seen in the initial chest radiograph. This observation is limited by the fact 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 is prudent for clinicians to closely monitor patients with advanced age, comorbidities or dyspnoea, especially at 1–2 weeks after symptom onset.

Interestingly, our patient remained in a semi-conscious state for almost 4 days without sedation and opioid therapy. No abnormalities were seen on brain CT and no significant metabolic disturbances could be found to explain the degree of unconsciousness. Subsequently, he regained full consciousness without any neurological deficit. Although septic encephalopathy is a likely diagnosis, it is also possible that this outcome could be attributed to the accumulation of fentanyl from

Table 2. Patient Outcomes from Coronavirus Disease 2019 Infection in Mainland China Who Required ICU Admission

Variable	Huang et al[*]	Chen et al[†]	Wang et al[‡]	Yang et al[§]	Guan et al[‖]
Centre(s)	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Zhongnan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	552 hospitals in 30 provinces
Hospitalisation/recruitment	16 Dec 2019 – 2 Jan 2020	1 – 20 Jan 2020	1 – 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
Number of patients	13	23	36	52	67[¶]
Median age in years (IQR)	49 (41 – 61)	NA	66 (57 – 78)	60 (13)	63 (53 – 71)
Comorbidity (%)					
Hypertension	15	NA	58	NA	NA
Diabetes mellitus	8	NA	22	17	36
Cardiovascular disease	23	NA	25	NA	27
Cerebrovascular disease	NA	NA	17	14	6
Chronic respiratory disease	8	NA	8	8	10
Symptom onset to ARDS in days, median (IQR)	9 (8 – 14)	NA	8 (6 – 12)	NA	NA
Symptom onset to ICU admission in days, median (IQR)	11 (8 – 17)	NA	10 (6 – 12)	10 (7 – 13)	NA
ICU outcome (%)					
Nosocomial infection	31	NA	NA	14	NA
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
Hospitalised at end of study	8	NA	58	23	76
On mechanical ventilation at end of study	NA	NA	17	1	NA

ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; IQR: Interquartile range; NA: Not available

[*]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.

[†]Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, 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.

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[§]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 2020;DOI:10.1016/S2213-2600(20)30079-5.

[‖]Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;DOI:10.1056/NEJMoa2002032.

[¶]Composite outcome of death, ICU admission or mechanical ventilation.

[#]28-day ICU mortality.

inhibition of cytochrome P450 by ritonavir, which is another important consideration for intensivists in their management of such patients.[24]

Outcomes and Mortality of Critical Illness from COVID-19 Infection

Critical illness from COVID-19 infection is associated with high mortality risk even though its estimated case fatality rate of 3.4%[2] is significantly lower than MERS-CoV (34.4%)[3] and SARS (11%).[25] In Jin Yin-Tan Hospital in Wuhan city, mortality rate of ICU patients was reported to range between 38–62% and >10% of patients required extracorporeal membrane oxygenation (ECMO).[9,10,12] Yang et al reported a 28-day mortality rate of 62% in patients who required ICU care; in patients who developed ARDS, the mortality rate was 74%.[12] In-hospital mortality rate was likely to be higher since most survivors were still hospitalised, 3 patients were on mechanical ventilation and 1 patient was on ECMO.[12] Indeed, the mortality rates that were being reported were alarming since they were higher than that commonly seen in severe ARDS attributed to other causes and conditions.[26]

It is possible, however, that the quality of health services was severely compromised and resulted in poorer outcomes in Wuhan city after health workers there were overwhelmed by the exponential increase in the number of COVID-19 patients. A recent publication by Xie et al reported severe shortages in ventilators and only about 25% of patients who died had received invasive mechanical intubation.[27] Additionally, most patients were supported with high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) and received systemic corticosteroids.[9,12] It is unclear whether delayed intubation or systemic corticosteroids might have adversely affected the outcomes in some patients.[28] As was the case with our patient, up to a third of critically ill patients developed nosocomial or secondary bacterial infections and intensivists who manage such patients must remain vigilant since early administration of antibiotics may potentially improve outcomes.[9,12] Finally, data is still lacking on duration of mechanical ventilation or ECMO in survivors since such information is important for critical care management and resource planning.

Clinical Management of Critical Illness from COVID-19 Infection

In the absence of studies on ARDS induced by COVID-19 infection, principles of clinical management of patients should be consistent with established guidelines for ARDS. The WHO has published similar guidelines for severe respiratory infections from COVID-19 infection.[29] In our patient, we adopted lung protective ventilation, conservative fluid strategy and neuromuscular blockade to manage moderate to severe ARDS. Neuromuscular blockade was initiated after significant ventilator dyssynchrony was seen despite deep sedation.

Since there was a lack of clear benefit with the use of HFNC in acute respiratory failure and high failure rates were observed with the use of NIV in MERS-CoV,[30] the management of our patient was therefore guided by the principles of conventional oxygen therapy and early intubation. The presumed benefit of lopinavir/ritonavir was extrapolated from the management of SARS patients.[31,32] Remdesivir—a broad-spectrum pro-drug that inhibits RNA-dependent RNA-polymerase activity—has shown promise in in vitro studies and is currently under evaluation in a randomised, controlled clinical trial (NCT04257656).[33]

To date, no antiviral therapy has proven effective against COVID-19 infection. In our patient, corticosteroids were not administered since there was a lack of evidence to support their efficacy;[34] The use of corticosteroids is associated with worse outcomes or delayed viral clearance in SARS and MERS-CoV patients.[35,36] Finally, infection control and prevention is a key component of ICU management.[37] The emphasis is on use of appropriate personal protective equipment and practice of standard contact and airborne precautions with eye protection by health workers. Known or suspected COVID-19 patients should be isolated in AIIR and measures to minimise aerosolisation or dispersion of respiratory droplets by patients should be stringently practised.[38]

Interestingly, our patient had diarrhoea and SARS-CoV-2 was detected in his stool samples. A small study of 8 patients by Young et al also reported that the stools of 4 of them tested positive for SARS-CoV-2 on RT-PCR.[19] These findings suggest that viral transmission through the faecal-oral route may be a concern in patients with COVID-19 infection.[39]

Conclusion

The wide clinical spectrum of COVID-19 infection ranges from individuals who are asymptomatic to those who present with critical illness and with high mortality risk. Since there is a likelihood that patients will deteriorate rapidly, more studies are needed to identify early predictive markers of the more severe form of the disease. In the absence of a clear, dysregulated host response to infection, abnormal laboratory findings such as lymphopaenia or elevated LDH may potentially serve as early surrogate markers for the development of

critical illness. While we await results of studies that can shed more light on definitive treatment options, management of ARDS induced by COVID-19 infection is mainly supportive and does not differ from that caused by other conditions other than a need to adhere strictly to established infection control measures.

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