Original Article

Characteristics and Outcomes of COVID-19 Patients with Respiratory Failure Admitted to a "Pandemic Ready" Intensive Care Unit – Lessons from Singapore

Si Yuan Chew, [1]*MBBS, MRCP*, Yee Shay Lee, [2]*MBBS, MRCP*, Deepak Ghimiray, [2]*MBBS*, Chee Keat Tan, [2]*MD, MMed (Anaes)*, Gerald SW Chua, [3]*MBBS, MRCP*

Abstract

Introduction: Singapore was one of the first countries affected by the coronavirus disease 2019 (COVID-19) pandemic but has been able to prevent its healthcare system and intensive care units (ICU) from being overwhelmed. We describe the clinical features, management and outcomes of COVID-19 patients with respiratory failure admitted to our ICU. Materials and Methods: A case series of COVID-19 patients admitted to our ICU for respiratory failure from 7 February, with data censoring at 30 June 2020, was performed from a review of medical records. Results: Twenty-two COVID-19 patients were admitted to our ICU for respiratory failure. The median age was 54.5 years (IQR 30–45.5), 72.7% were male and had at least one comorbidity. The Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were 2.5 (IQR 1.25–7) and 10 (8.25–12) respectively. Thirteen patients required invasive mechanical ventilation (IMV) and had a median PaO2/FiO2 ratio of 194 mmHg (IQR 173–213) after intubation. The 28-day survival was 100%, with 2 patients demising subsequently. The overall ICU mortality rate was 9.1% at the time of data censoring. In IMV survivors, length of IMV and ICU stay were 11 days (IQR 9–17.75) and 16 days (IQR 12–32) respectively. Conclusion: Low COVID-19 ICU mortality was observed in our "pandemic-ready" ICU. This was achieved by having adequate surge capacity to facilitate early ICU admission and IMV, lung protective ventilation, and slow weaning. Being able to maintain clinical standards and evidence-based practices without having to resort to rationing contributed to better outcomes.

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Key Words: Acute respiratory distress syndrome, Coronavirus, Critical care, Pandemic, Pneumonia

Introduction

An outbreak of coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China on 31 December 2019[1] and was soon declared a global pandemic on 11 March 2020 by the World Health Organisation (WHO).[2] Although most infections are mild, initial studies from pandemic epicentres have reported a significant incidence of critical illness amongst hospitalised patients: China (17–29%),[3–6] Italy (16%),[7] and New York (14.2%).[8] Worryingly, early case series of COVID-19 patients admitted to intensive care units (ICU) suggest that many do not survive. In Wuhan, 28-day ICU mortality was reported as 61.5%[4] while case series of ICU patients with COVID-19 from New York, Seattle and Washington have reported ICU mortality rates of 22.7%[8] 50%[9] and 67%[10] respectively.

Despite being one of the first countries to be affected by the pandemic, COVID-19 mortality in Singapore remains low. With 26 deaths occurring

[1] Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore
[2] Department of Intensive Care Medicine, Ng Teng Fong General Hospital, Singapore
[3] Department of Medicine, Ng Teng Fong General Hospital, Singapore
Address for Correspondence: Dr Chew Si Yuan, Department of Respiratory and Critical Care Medicine, Level 3, Academia, Singapore General Hospital, Outram Rd, Singapore 169608.
Email: chewsiyuan@gmail.com

in 43,881 laboratory-confirmed cases on 30 June 2020,[11] Singapore has a case fatality rate (CFR) of 0.059% compared to the global CFR of 4.95%.[12] While differences in patient characteristics, availability of reliable testing and case definitions may account for the markedly lower fatality rate in Singapore,[13] there is no doubt that rapid overwhelming of the healthcare systems in the pandemic epicentre of Wuhan contributed directly to higher mortality. Due to shortages of ICU equipment in Wuhan, it was estimated that only 25% of patients who died received intubation or mechanical ventilation.[14] Fortunately, Singapore has been able to stay ahead of the curve thanks to early travel restrictions, social distancing measures and aggressive contact tracing and testing at the national level.[15] To rapidly expand healthcare capacity, hospitals postponed non-urgent elective procedures, transferred stable patients to step-down care facilities and repurposed existing wards into isolation facilities. On 4 May 2020, the Minister of Health, Singapore updated Parliament that Singapore had 150 vacant ICU beds currently, with the ability to add a further 450 ICU beds by mid-May if required.[16] At that time, Singapore had reported 22 critically ill COVID-19 patients in ICU. ICU capacity in Singapore therefore remained adequate throughout. In our single-centre case series, we describe the characteristics and outcomes of COVID-19 patients admitted to an ICU in Singapore whose capacity remains unstressed.

Materials and Methods

Ng Teng Fong General Hospital is a 700 bed hospital with a multidisciplinary medical-surgical ICU that was built 5 years ago with the facilities to manage a pandemic or mass casualty event. The ICU consists of 74 single rooms divided into 5 pods, of which only 2 pods were in full-time use prior to the pandemic. If required, each room was equipped with the space, medical gas outlets, and electrical systems on 2 pendants to accommodate 2 patients on invasive mechanical ventilation (IMV) in a surge crisis situation. It is accredited by the College of Intensive Care Medicine of Australia and New Zealand and is staffed by a department comprising specialist intensivists and non-specialist physicians. At the start of the pandemic, there were 7 full-time intensivists that provided 24-hours stay-in specialist coverage. This was increased to 13 full-time intensivists through full-time re-deployment of anaesthetists, respiratory and emergency medicine physicians, who have been practising intensive care medicine on a 50% full-time equivalence basis prior to the pandemic. Non-specialist physician and nurse staffing was also augmented by re-deployment of specialists, junior physicians and nurses from the department of anaesthesia. The Acute Physiology and Chronic Health Evaluation (APACHE) II standardised mortality ratio of our ICU in 2018 was 0.77. From the beginning, it was decided to implement segregation of ICU staffing, physical areas, and processes for usual ICU patients and COVID-19 patients to mitigate against nosocomial transmission of COVID-19. One pod of 12 negative-pressure single rooms was designated as the "pandemic ICU" dedicated to confirmed or suspect COVID-19 patients, and capacity was never exceeded. This was furnished with an adjoining shower facility for staff and 6 of these rooms were equipped with an anteroom. This pandemic ICU was staffed around the clock by a stay-in specialist intensivist supported by at least 2 junior doctors. All COVID-19 patients received at least one-to-one level of nursing.

All patients had a laboratory diagnosis of COVID-19 based on real-time reverse transcriptase–polymerase chain reaction testing on nasopharyngeal swab or endotracheal aspirate samples. Patients were admitted to our ICU if they met WHO criteria for severe pneumonia, which comprised fever or suspected respiratory infection, plus 1 of respiratory rate >30 breaths per minute, severe respiratory distress or oxygen saturation <90% on room air.[17] Evidence-based guidelines for acute respiratory distress syndrome (ARDS)[18] as well as emerging consensus statements for critical care management of COVID-19[19–22] were applied. Non-intubated oxygen-dependent patients were asked to adopt prone positioning (PP) for as long as tolerated based on protocols from small case series that have described short-term physiological improvements in oxygenation.[23–25]

All patients requiring IMV received lung protective ventilation with Assist Control Volume Control mode with initial tidal volume of 6 ml/kg predicted body weight (PBW). Subsequent adjustments to tidal volume, if required, were kept between 6–8 ml/kg (PBW) and care was taken to keep plateau and driving pressures below than 30 cm H_2O and 15 cm H_2O respectively. Patients with moderate severity ARDS were managed with early neuromuscular blockade and PP. Pressure support ventilation (PSV) or airway pressure release ventilation (APRV) modes were used for ventilator weaning with or without tracheostomy. Heat-moisture-exchanger (HME) filters were used to humidify inspired gases and serve as a viral filter. Water-bath heated humidifiers

were not used due to theoretical risk of aerosol generation. All patients received thromboembolic prophylaxis with mechanical calf compressors and heparin (either subcutaneous enoxaparin 40 mg once daily or subcutaneous unfractionated heparin 5,000 units 3 times daily).

The de-identified clinical data of patients admitted to our intensive care unit was collected through a retrospective medical record review from 7 February 2020 to 7 June 2020. The ethics committee of National Healthcare Group (Domain Specific Review Board Reference: 2020/00704) approved this study and waived the requirement for informed consent due to the nature of retrospective medical record review. Clinical data was recorded into a datasheet with data censoring on 30 June 2020. Continuous variables were expressed as median and interquartile range (IQR) and categorical variables as frequency and percentage. No analysis for statistical significance was performed given the descriptive nature of the study.

Results

Baseline Clinical Characteristics

Twenty-six COVID-19 patients were admitted to the pandemic ICU during the study period (Fig. 1). The primary indication for ICU admission was oxygen-dependent respiratory failure in 22 patients and their demographic, baseline clinical characteristics and laboratory results are shown in Table 1. The median age was 54.5 years (IQR 51–59). Nine (40.9%) patients were migrant workers while the rest were Singapore residents. Fifteen patients were admitted to the general ward initially and the median duration between hospitalisation and ICU admission was 4 (IQR 2.5–5) days. The median number of days from symptom onset to ICU admission and requirement for intubation was 8 (IQR 5.5–8) days and 9 (IQR 7–9) respectively. Sixteen (72.7%) patients had at least 1 comorbidity. The most common comorbidities were hypertension (10, 45.5%) and diabetes mellitus (7, 31.8%). The median body

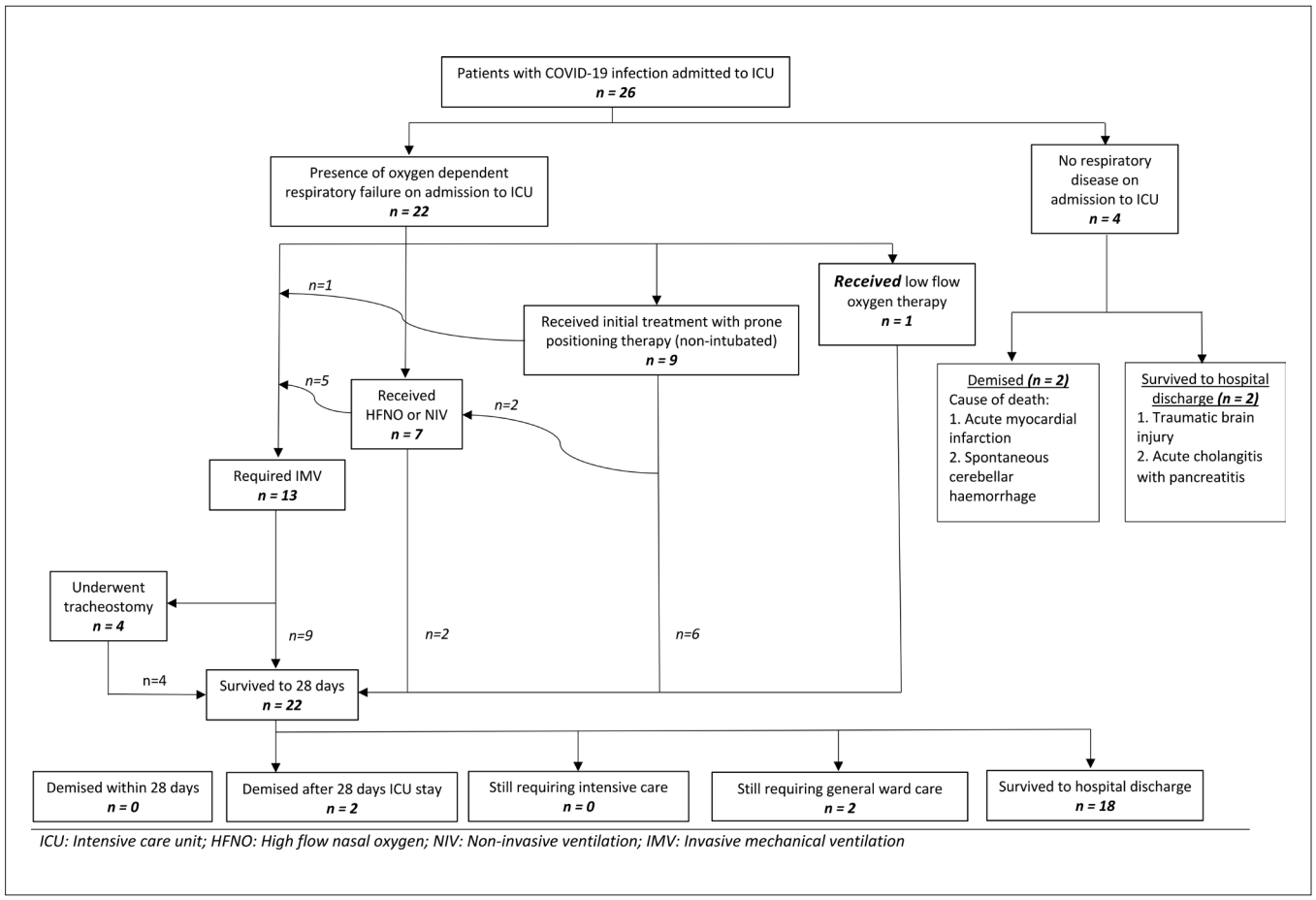

Fig.1. Indications for Admission, Initial Ventilatory Treatment and Outcomes of all COVID-19 Patients Admitted to the ICU

Table 1. Baseline Characteristics of COVID-19 Patients with Respiratory Failure admitted to the ICU

Demographics	***n = 22***	
Median age (IQR)	54.5 (30–45.5)	
Age <50 years	7 (31.8%)	
Age 50 – 60 years	10 (45.5%)	
Age 60 – 70 years	2 (9.1%)	
Age >70 years	3 (13.6%)	
Male gender	16 (72.7%)	
Residential status and ethnicity		
Local resident, Chinese	8 (36.3%)	
Local resident, Malay	5 (22.7%)	
Migrant worker	9 (40.9%)	
Comorbidities	**No. (%) of patients *(n = 22)***	
Hypertension	10 (45.5%)	
On ACE-I or ARB	6 (27.2%)	
Diabetes mellitus	7 (31.8%)	
Hyperlipidaemia on treatment with statins	6 (27.2%)	
Chronic kidney disease	4 (18.2%)	
Chronic lung disease	2 (9.1%)	
Total with ≥1 comorbidity	16 (72.7%)	
BMI (IQR)	26 (23.1 – 32.6)*	
Overweight (defined as BMI ≥25)	3 (13.6%)	
Obesity (defined as BMI ≥30)	6 (27.2%)	
Clinical presentation on admission to hospital	**No. (%) of patients *(n = 22)***	
Fever	20 (90.9%)	
Cough	17 (77.2%)	
Dyspnoea	4 (18.1%)	
Admission characteristics		
Admission to general ward prior to admission to ICU	15 (68.2%)	***n = 22***
Median time between hospital and ICU admission (days)	4 (2.5 – 5)	***n = 15***
Median number of days from symptom onset of requirement for supplemental oxygen (IQR)	8 (5.5 – 8)	***n = 22***
Median number of days from symptom onset to admission to ICU (IQR)	8 (5.5 – 9)	***n = 22***
Median number of days from symptom onset to requirement for intubation (IQR)	9 (7 – 9)	***n = 13***
Laboratory tests at time of admission to ICU, mean (range)		**Reference range**
Haemoglobin, (range)	13.7 (8.8 – 14.5)	13.1 – 17.2 g/dL
White blood cell count, (range)	8.32 (3.96 – 25.95)	3.37 – 11.03 x 10^9/L
Presence of lymphopenia (defined as <0.98 x 10^9/L)	16 (72.7%)	***n = 22***
Absolute lymphocyte count at nadir (range)	0.76 (0.06 – 1.28)	0.86 – 3.88 x 10^9/L

ACE-I: Angiotensin converting enzyme Inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; ICU: Intensive care unit
*No data available for 3 patients.

Table 1. Baseline Characteristics of COVID-19 Patients with Respiratory Failure admitted to the ICU (Cont'd)

Demographics	***n = 22***	
Presence of thrombocytopenia	9 (40.9%)	<172 x 10^9/L
Urea, (range)	7.49 (2 – 30.7)	2.8 – 7.6 mmol/L
Sodium, (range)	134 (127 – 145)	134 – 146 mmol/L
Creatinine, (range)	139 (29 – 704)	64 – 104 umol/L
Total bilirubin, (range)	13.8 (2.1 – 65.3)	4.7 – 23.2 umol/L
Alkaline phosphatase, (range)	85.4 (38 – 186)	10 – 34 U/L
Alanine aminotransferase, (range)	64.2 (10 – 354)	<55 U/L
Aspartate aminotransferase, (range)	102.9 (17 – 875)	10 – 34 U/L
C-reactive peptide, (range)	149.7 (49 – 356)	0.0 – 5.0 mg/L
Procalcitonin, (range)†	2.19 (0.02 – 14.3)	<0.50 ng/mL
Lactate dehydrogenase, (range)†	536 (176 – 1001)	270 – 550 U/L
Ferritin, (range)‡	1995 (332 – 6732)^	4.6 – 204 ng/mL
Elevated high sensitivity Troponin I > 34.2 pg/ml	1 (4.5%)	***n = 22***
Evidence of co-infection (%)	4 (18.2%)	***n = 22***

ACE-I: Angiotensin converting enzyme Inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; ICU: Intensive care unit
†No data available for 2 patients.
‡No data available for 5 patients.

mass index (BMI) was 26 (IQR 23.1–32.6), with 3 (13.6%) and 6 (27.2%) patients meeting WHO criteria for overweight and obesity. Four patients had evidence of bacterial co-infection on microbiological culture.

Characteristics and Outcomes of Patients receiving PP (non-intubated) and High-flow Nasal Oxygen (HFNO) Therapy

Nine non-intubated patients (40.9%) received initial treatment on ICU admission with PP for a median duration of 2 (IQR 1–4) days (Table 2). Their median values for Sequential Organ Failure Assessment (SOFA), APACHE II was 1 (IQR 1–2) and 9 (IQR 8–10) respectively. The median arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio was 241 mmHg (IQR 223–286) at baseline and 325 mmHg after 30–180 minutes. Patients tolerated a median duration of 10 hours of PP on day 1. Two patients eventually required IMV and 1 patient required a combination of non-invasive ventilation (NIV) and HFNO therapy (Fig.1). Seven patients received initial treatment with HFNO with 5 patients requiring IMV subsequently.

Characteristics of Patients receiving IMV

Thirteen (59%) patients in total received IMV (Table 2). At time of intubation, the median SOFA and APACHE II scores were 7 (IQR 5–8) and 13 (IQR 10–23) respectively. The median PaO_2/FiO_2 ratio immediately after intubation was 194 mmHg (IQR 173–213) with all patients fulfilling the Berlin criteria for ARDS of moderate severity.[26] Patients on IMV received a median positive end-expiratory pressure (PEEP) of 11 (IQR 10–14) on day 1, with all patients receiving neuromuscular blockade for a median of 3 days (IQR 2–3). The mean plateau and driving pressures were 22.5 cm H_2O (IQR 20.5–25) and 10 cm H_2O (IQR 8–12) respectively on day 1 IMV. Static respiratory compliance was 29 ml/cm H_20 (IQR 27.5–35.4). Seven (53.8%) patients received PP with before and after PaO_2/FiO_2 ratios of 127 mmHg (IQR 127–137.5) and 201 mmHg (IQR 170.5–238.5) respectively. One patient required extracorporeal membrane oxygenation (ECMO) therapy for 30 days and was successfully weaned from ECMO and IMV to nocturnal NIV at the time of data censoring. All patients received investigational COVID-19 therapy. Table 3 lists individualised case summaries and outcomes of patients requiring IMV

Table 2. Clinical Course, Treatment and Outcomes of COVID-19 Patients with Respiratory Failure

SOFA score at time of ICU admission (IQR)	2.5 (1.25 – 7)	***n = 22***
APACHE II score at time of ICU admission (IQR)	10 (8.25 – 12)	
Underwent non-intubated prone positioning (%)	9 (40.9%)	
Use of non-invasive ventilation (%)	1 (4.5%)	
Use of high flow nasal oxygen therapy (%)	7 (31.8%)	
Required invasive mechanical ventilation (%)	13 (59.1%)	
Required vasopressors (%)	13 (59.1%)	
Use of steroid therapy (%)	5 (22.7%)	
Among 9 patients who received initial prone positioning therapy (non-intubated)		***n = 9***
SOFA score (IQR)	1 (1 – 2)	
APACHE II score (IQR)	9 (8 – 10)	
PaO_2/FiO_2 ratio (IQR) prior to prone positioning	241 (233 – 286)	
PaO_2/FiO_2 ratio (IQR) 30-180 minutes after prone positioning	325 (254 – 380)	
A-a gradient prior to prone positioning	87.7 (84.1 – 94.8)	
A-a gradient 30-180 minutes after prone positioning	72.9 (56.7 – 84.7)	
Duration of prone positioning therapy in days (IQR)	2 (1 – 4)	
Number of hours of prone position tolerated by patient on day 1 (IQR)	10 (3 – 10)	
Longest continuous duration of prone position tolerated in hours (IQR)	4 (3 – 7)	
Required invasive mechanical ventilation (%)	2 (22.2%)	
Survival at 28 days from ICU admission	8 (88.9%)	
Survivors discharged from ICU, median ICU length of stay, days (IQR)	5 (3.25 – 6)	***n = 8***
Survivors discharged from hospital, median hospital length of stay, days (IQR)	18 (14 – 19)	***n = 7***
Among patients requiring invasive mechanical ventilation	**13 (59.1%)**	***n = 13***
Intubation performed in the Emergency Department	2 (15.4%)	
Intubation performed in ICU	11 (84.6%)	
SOFA score at time of initiation of IMV (IQR)	7 (5 – 8)	
APACHE II score at time of initiation of IMV (IQR)	13 (10 – 23)	
PaO_2/FiO_2 ratio (IQR)		
Immediately after intubation (mmHg)	194 (173 – 213)	
Nadir (mmHg)	136 (125 – 141.5)*	
A-a oxygen gradient after intubation	179.9 (167.5 – 209.2)	
Median level of positive end-expiratory positive pressure on day 1 invasive mechanical ventilation, cm H_2O (IQR)	11 (10 – 14)	

A-a gradient: Alveolar-arterial gradient; APACHE II: Acute physiology and chronic health evaluation II; DVT: Deep vein thrombosis; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IQR: Interquartile range; PaO_2: Partial pressure of oxygen in arterial blood; PE: Pulmonary embolism; SOFA: Sequential organ failure assessment

†Excluding 1 patient who is currently still dependent on nocturnal non-invasive ventilation

[1]Defined by criteria from the Kidney Disease Improving Global Outcomes and the International Society of Nephrology.

[2]Defined as an alanine aminotransferase or aspartate aminotransferase level greater than 3 times the upper limit of normal.

Table 2. Clinical Course, Treatment and Outcomes of COVID-19 Patients with Respiratory Failure (Cont'd)

Highest median fraction of inspired oxygen requirement on day 1 invasive mechanical ventilation, (range)	45% (40 – 52.5%)	
Highest level of positive end-expiratory positive pressure applied during invasive mechanical ventilation, cm H_2O (IQR)	14 (14 – 16)	
Plateau pressure on day 1 invasive mechanical ventilation, cm H_2O (IQR)	22.5 (20.5 – 25)	
Driving pressure on day 1 invasive mechanical ventilation, cm H_2O (IQR)	10 (8 – 12)	
Static respiratory compliance on day 1 of invasive mechanical ventilation, ml/cm of water (IQR)	29 (27.5 – 35.4)*	
Use of neuromuscular blockade (%)	13 (100%)	
Median number of days neuromuscular blockade (IQR)	3 (2 – 3)	
Use of prone positioning (%)	7 (53.8%)	
PaO_2/FiO_2 ratio prior to prone therapy	127 (121 – 137.5)	
PaO_2/FiO_2 ratio after prone therapy	201 (170.5 – 238.5)	After first session of prone therapy
A-a gradient prior to prone therapy	183 (170.5 – 226.5)	
A-a gradient after prone therapy	151 (101 – 204)	After first session of prone therapy
Absolute increase in PaO_2 after prone positioning (mmHg)	15.1 (11.4 – 38.4)	After first session of prone therapy
Use of extra-corporeal membrane oxygenation	1 (7.7%)	
Underwent tracheostomy	4 (30.8%)	
Presence of complications in patients on IMV		***n = 13***
Pneumothorax (%)	1 (7.7%)	
Ventilator associated pneumonia (%)	5 (38.5%)	
Median days from intubation to onset	5 days	
Acute kidney injury[1]	9 (69.2%)	
Required renal replacement therapy	7 (53.8%)	
Airway complications requiring re-intubation	3 (23.1%)	
Endotracheal tube obstruction by secretions	2 (15.4%)	
Endotracheal tube cuff leak	1 (7.7%)	
Deranged liver function tests[2]	6 (46.2%)	
Acute cardiac injury / cardiomyopathy	1 (7.7%)	
Venous thromboembolism (DVT or PE)	2 (15.4%)	
COVID-19 related encephalopathy	1 (7.7%)	
Investigational anti-viral therapy administered		
Lopinavir/ritonavir	7 (53.8%)	

A-a gradient: Alveolar-arterial gradient; APACHE II: Acute physiology and chronic health evaluation II; DVT: Deep vein thrombosis; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IQR: Interquartile range; PaO_2: Partial pressure of oxygen in arterial blood; PE: Pulmonary embolism; SOFA: Sequential organ failure assessment

†Excluding 1 patient who is currently still dependent on nocturnal non-invasive ventilation

[1]Defined by criteria from the Kidney Disease Improving Global Outcomes and the International Society of Nephrology.

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Table 2. Clinical Course, Treatment and Outcomes of COVID-19 Patients with Respiratory Failure (Cont'd)

Beta-interferon	3 (23.1%)	
Hydroxychloroquine	3 (23.1%)	
Tocilizumab	3 (23.1%)	
Convalescent plasma	2 (15.4%)	
Outcomes of patients requiring IMV		
Survival at 28 days from ICU admission	13 (100%)	***n = 13*** *1* patient demised on day 30 of ICU stay and 1 patient demised on day 31 of ICU stay
Remains dependent on mechanical ventilation	1 (7.7%)	***n = 13***
Re-intubation rate	3 (23.1%)	***n = 13***
Survivors extubated from invasive mechanical ventilation (IMV), Median duration of IMV in days (IQR)	11 (9 – 17.75)	***n = 10***†
Survivors discharged from ICU, median ICU length of stay, days (IQR)	16 (12 – 32)	***n = 11***
Survivors discharged from hospital, length of hospitalisation in days (IQR)	40 (32 – 50)	***n = 9***

A-a gradient: Alveolar-arterial gradient; APACHE II: Acute physiology and chronic health evaluation II; DVT: Deep vein thrombosis; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; IQR: Interquartile range; PaO_2: Partial pressure of oxygen in arterial blood; PE: Pulmonary embolism; SOFA: Sequential organ failure assessment
†Excluding 1 patient who is currently still dependent on nocturnal non-invasive ventilation
[1]Defined by criteria from the Kidney Disease Improving Global Outcomes and the International Society of Nephrology.
[2]Defined as an alanine aminotransferase or aspartate aminotransferase level greater than 3 times the upper limit of normal.

Patient Outcomes

All 22 patients with respiratory failure survived to 28 days from ICU admission. At time of data censoring, 2 patients (Table 3—Patients 8 and 11) demised on ICU day 30 and 31 respectively, 2 patients continue to require general ward care and 18 patients survived to hospital discharge. The median duration of IMV and ICU stay in survivors was 11 days (IQR 9–17.75) and 16 days (IQR 12–32). Four patients required tracheostomy for prolonged IMV. Nine patients developed acute kidney injury with seven patients requiring haemodialysis. Five patients developed ventilator associated pneumonia and 2 patients developed sudden endotracheal tube obstruction by secretions requiring emergency re-intubation. All patients received venous thromboembolic (VTE) prophylaxis with heparin and did not develop VTE during their ICU stay. However, 2 patients who did not require IMV subsequently developed VTE during convalescence in general ward. One patient was still on heparin prophylaxis when he was diagnosed with pulmonary embolism 15 days after ICU admission. In the second patient, heparin prophylaxis was discontinued 2 days prior to the diagnosis of pulmonary embolism 12 days after ICU admission.

Discussion

In our single centre case series, all 22 COVID-19 patients admitted to our ICU for respiratory failure survived to 28 days, although 2 patients subsequently demised, giving an overall ICU mortality rate of 9.1%. ICU mortality of 13 patients requiring IMV was 15.4%. This is in marked contrast from reported ICU mortality rates from large case series from various countries: China 49%,[27] Lombardy, Italy, 26%,[28] United Kingdom 43.2%,[29] Scotland 38%,[30] Atlanta, Georgia, United States, 30.9%.[31]

Various reasons could account for the significant differences in ICU outcomes. Firstly, at the time of reporting, many patients remain admitted in the ICU—58% of patients in the Lombardy cohort[28] and 56.1% of patients in the New York case series.[8] Attempts to measure mortality at the early phase of the pandemic based on a smaller group of patients with completed outcomes with a short duration of follow-up could

Table 3. Clinical Features, Respiratory Mechanics and Complications of COVID-19 Patients with Respiratory Failure requiring Invasive Mechanical Ventilation

No.	Age (years), Gender, Ethnicity	Comorbidities	Day of Illness at time of IMV	Prognostic Scores at initiation of IMV		Oxygenation Status Before and After Initiation of IMV				Respiratory Mechanics					Clinical Features			Ventilator mode during Weaning	Complications	28 Day Survival	ICU Length of Stay (Days)
				SOFA Score	APACHE II Score	PaO_2/FiO_2 Ratio		A-a Gradient		PEEP	FiO_2	Plateau Pressure cm H_2O	Driving Pressure cm H_2O	Respiratory Compliance ml/cm H_2O	Presence of co-infection at admission	Prone Therapy	Anti-viral therapy				
						Before IMV	After IMV	Before IMV	After IMV												
1	52, Male, local resident Chinese	DM, HL, HTN, Obesity BMI 33.6	Day 9	9	8	81	167	589	176	15	40%	28	13	NA	Nil	Nil	Lopinavir-Ritonavir for 10 days	PSV only	Nil	Yes	8
2	57, Female, local resident Chinese	None, BMI 24.8	Day 16	11	9	105	194	329	165	15	40%	26	12	39	Yes (UTI and false positive dengue serology)	Nil	Lopinavir-Ritonavir for 10 days and Beta-interferon (6 doses)	PSV only	VAP (Day 11 IMV); AKI not requiring RRT	Yes	21
3	66, Male, local resident Chinese	HL, HTN, BMI 24.9	Day 9	5	10	122	154	255	221	14	50%	25	9	44.1	Nil	Yes (Days 6-8 of IMV)	Lopinavir-Ritonavir for 6 days and Beta-interferon (4 doses)	PSV and APRV	VAP (Days 4 and 13 IMV); Required exchange of ETT due to obstruction from secretions; Tracheostomy (Day 15 IMV)	Yes	33
4	68, Female, local resident Chinese	HL, HTN, BMI 29.2	Day 8	7	12	122	281	260	86	10	35%	18	8	39	Nil	Yes (Days 1-2 of IMV)	Lopinavir-Ritonavir for 14 days and Beta-interferon (7 doses)	APRV	Nil	Yes	16
5	57, Female, local resident Chinese	Scoliosis causing restrictive lung disease with chronic respiratory failure, BMI 21.4	Day 2	11	13	103	211	511	180	10	45%	22	12	23.9	Nil	Yes (Days 3-7 of IMV)	Lopinavir-Ritonavir for 4 days	Unable to wean off IMV	AKI requiring RRT; Myocarditis; Required exchange of ETT due to obstruction from secretions	Yes	85 (still requiring nocturnal NIV)

Table 3. Clinical Features, Respiratory Mechanics and Complications of COVID-19 Patients with Respiratory Failure requiring Invasive Mechanical Ventilation (Cont'd)

No.	Age (years), Gender, Ethnicity	Comorbidities	Day of Illness at time of IMV	Prognostic Scores at initiation of IMV		Oxygenation Status Before and After Initiation of IMV				Respiratory Mechanics					Clinical Features			Ventilator mode during Weaning	Complications	28 Day Survival	ICU Length of Stay (Days)
				SOFA Score	APACHE II Score	PaO_2/FiO_2 Ratio		A-a Gradient		PEEP	FiO_2	Plateau Pressure cm H_2O	Driving Pressure cm H_2O	Respiratory Compliance ml/cm H_2O	Presence of co-infection at admission	Prone Therapy	Anti-viral therapy				
						Before IMV	After IMV	Before IMV	After IMV												
7	71, Male, local resident Chinese	DM, HL, Obesity BMI 32.1	Day 4	7	10	55	213	621	170	12	45%	23	11	36	Nil	No	Lopinavir-Ritonavir for 8 days with HCQ for 3 days	APRV then PSV	VAP (Days 4 and 10 IMV); AKI not requiring RRT; Tracheostomy (Day 18 IMV)	Yes	31
8	58, Female, local resident Malay	DM, Obesity BMI 35.7	Day 11	5	9	76	180	347	201	14	50%	23	11	28.1	Yes (Pneumococcal and klebsiella pneumonia)	No	HCQ for 7 days	Patient demised	VAP (Days 5 and 14 IMV); AKI requiring RRT; Required exchange of ETT due to cuff leakage Tracheostomy (Day 14 IMV)	Demised on ICU day 30. Developed recurrent seizures associated with raised intracranial pressure with subsequent progression to brain death.	
9	59, Male, migrant worker (Thailand)	Newly diagnosed CKD, BMI 21.3	Day 3	8	24	97.8	217	602	168	8	45%	21	13	28	Yes (Staph aureus pneumonia)	Yes (Days 3-4 of IMV)	Convalescent plasma therapy on day 6 of illness	APRV with extubation to HFNO	AKI requiring RRT	Yes	13
10	40, Male, migrant worker (Myanmar)	None, BMI 23.3	Day 7	6	8	134	194	247	209	10	50%	25	15	29	Nil	Yes (Days 1-3 of IMV)	Convalescent plasma therapy on day 11 of illness	APRV then PSV with extubation to HFNO	Nil	Yes	16

Table 3. Clinical Features, Respiratory Mechanics and Complications of COVID-19 Patients with Respiratory Failure requiring Invasive Mechanical Ventilation (Cont'd)

No.	Age (years), Gender, Ethnicity	Comorbidities	Day of Illness at time of IMV	Prognostic Scores at initiation of IMV		Oxygenation Status Before and After Initiation of IMV				Respiratory Mechanics					Clinical Features			Ventilator mode during Weaning	Complications	28 Day Survival	ICU Length of Stay (Days)
				SOFA Score	APACHE II Score	PaO_2/FiO_2 Ratio		A-a Gradient		PEEP	FiO_2	Plateau Pressure cm H_2O	Driving Pressure cm H_2O	Respiratory Compliance ml/cm H_2O	Presence of co-infection at admission	Prone Therapy	Anti-viral therapy				
						Before IMV	After IMV	Before IMV	After IMV												
11	51, Male, migrant worker (China)	None, BMI 22.9	Day 20	7	23	165	214	187	206	10	50%	18	8	68	Nil	Yes (Days 2-4 of IMV)	Tocilizumab on days 17 and 20 of illness	Patient demised	AKI requiring RRT; Developed HLH associated with EBV associated NK T cell lymphoma diagnosed on bone marrow biopsy on day 16 of illness	Demised on ICU day 31. Developed recurrent neutropenic sepsis (candidemia, Pseudomonas and Ralstonia bacteremia) leading to eventual demise.	
12	43, Male, local resident Malay	HTN, CKD, previous DVT, BMI 26.4	Day 8	11	23	73.1	191	615	296	18	70%	26	8	26	Nil	Yes (Day 1 of IMV)	Tocilizumab on day 9 of illness	PSV	VAP (Day 16 IMV); tracheostomy (Day 13 IMV); AKI requiring RRT, Developed recurrent lower gastrointestinal haemorrhage on day 26 of illness requiring right hemicolectomy	Yes	44
13	51, Male, migrant worker (Myanmar)	Newly diagnosed DM, BMI 24.9	Day 9	3	15	112	173	265	161	10	40%	19	9	39	Yes (Staph aureus and Klebsiella pneumonia)	No	Tocilizumab on day 9 of illness	PSV	Nil	Yes	6

A-a gradient: Alveolar-arterial gradient; AKI: Acute kidney injury; APACHE II: Acute physiology and chronic health evaluation; APRV: Airway pressure release ventilation; CKD: Chronic kidney disease; cm H_2O: Centimetres of water pressure; DM: Diabetes mellitus; DVT: Deep vein thrombosis; ETT: Endotracheal tube; FiO_2: Fraction of inspired oxygen; HCQ: Hydroxychloroquine; HFNO: High flow nasal oxygen; HL: Hyperlipidaemia; HLH: Hemophagocytic lymphohistiocytosis; HTN: Hypertension; IMV: Invasive mechanical ventilation; IQR: Interquartile range; ml/cm H_2O: Millilitres per centimetre of water pressure; NA: Not available; NIV: Non-invasive ventilation; PaO_2: Partial pressure of oxygen in arterial blood; PE: Pulmonary embolism; PEEP: Positive end-expiratory pressure; PSV: Pressure support ventilation; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia

skew statistical interpretation in favour of higher mortality rates. In a more recent systematic review of 15 studies, it was found that the pooled ICU mortality rate was 25.7%,[32] which is not higher than the typical 35–45% mortality rate of ARDS.

Secondly, our patients had a lower risk profile for severe disease compared to data available from various large case series (Table 4). This may be related to differences in criteria for ICU admission. We applied the WHO criteria for severe pneumonia for ICU admission, while ICUs in overwhelmed healthcare systems might have applied more stringent admission criteria as part of rationing. Our patients were younger with a median age of 54.5 years compared to the median ages of 63 years in the Lombardy cohort, and 60 years in the Intensive Care National Audit and Research Centre (ICNARC) report for the United Kingdom.[29] Our patients also had lower ICU prognostication scores at ICU admission compared to other cohorts. Our overall median SOFA and APACHE II score on admission to ICU was 2.5 (IQR 1.25–7) and 10 (IQR 8.23–12) respectively. This is in contrast to the median APACHE II score of 17 (IQR 14–19) in a Wuhan cohort,[4] the median APACHE II score of 14 (IQR 11–18) in the ICNARC report,[29] the median APACHE II score of 15 in the Scottish Intensive Care Society Audit Group (SICSAG) report[30] and the median SOFA score of 7 (IQR 5–11) for the Atlanta cohort.[31] Finally, the severity of ARDS in our patients was milder compared to the other patient cohorts. The median PaO_2/FiO_2 ratio of our patients who required IMV was 194 (IQR 173–213) while patients from Lombardy,[28] the United Kingdom[29] and Atlanta[31] had lower PaO_2/FiO_2 ratios of 160 (IQR 114–220), 118.5 (IQR 84.8–165) and 132 (IQR 100–178) respectively. The lower risk profile of our patients could be attributed to the high proportion of migrant workers (40%) in our case series. This reflected the nature of the pandemic in Singapore, which disproportionately affected thousands of migrant workers who lived in crowded dormitories.[33] Migrant workers in Singapore comprise largely of young men who have little or no medical comorbidities, and are predominantly employed in the construction industry. Finally, higher body mass index (BMI) has been associated with more severe COVID-19 disease[34] and our patients had a lower median BMI of 26 compared to the median BMI of 30 (IQR 26–35) in the Atlanta cohort.[34]

Thirdly, our ICU capacity was never overwhelmed at any stage of the pandemic and did not have to practice rationing of ICU resources. There was therefore no pressure on our intensivists to perform

Table 4. Comparison of Admission Characteristics and Outcomes of COVID-19 Patients Admitted to the ICU

	NTFGH, Singapore	Lombardy, Italy; Grasselli et al[28]	United Kingdom; ICNARC Report[29]	Scotland; SICSAG Report[30]	Atlanta, Georgia, USA; Auld et al [31]
Cohort size	22	1581	8062	504	217
ICU mortality (%)	9.1	26	43.2	38	30.9
Median age, years (IQR)	54.5 (51 – 59)	63 (56 – 70)	60 (51 – 68)	60 (53 – 67)	64 (54 – 73)
Male gender (%)	72.7	82	70.9	71.8	54.8
Presence of any co-morbidity (%)	72.7	68	NA	28.1	NA
Median SOFA Score (IQR)	2.5 (1.25 – 7)	NA	NA	NA	7 (5 – 11)
Median APACHE II Score (IQR)	10 (8.23 – 12)	NA	14 (11 – 18)	15	NA
Received IMV (%)	59.1	88	72.2	81	76
Median PaO_2/FiO_2 ratio, mmHg (IQR)	194 (173 – 213)*	160 (114 – 220)	118.5 (84.8 – 165)	114 (83.3 – 157.5)	132 (100 – 178)

APACHE II: Acute physiology and chronic health evaluation; FiO_2: Fraction of inspired oxygen; IQR: Interquartile range; NA: Not available; NTFGH: Ng Teng Fong General Hospital; PaO_2: Partial pressure of oxygen in arterial blood; SOFA: Sequential organ failure assessment.
*For patients who received invasive mechanical ventilation.

high-risk extubations on our patients to free up ICU beds and ventilators. To date, the highest occupancy rate of our pandemic ICU was seven out of thirteen beds. In a case series of 109 COVID-19 decedents in Wuhan,[35] all of whom required critical care, it was reported that only 46.8% patients were eventually admitted to ICU due to resource constraints. Ventilators were also in short supply as evidenced by only 64.7% of ICU patients receiving IMV. Similarly, in Scotland, it was reported that the baseline capacity for the highest level of complex ICU care was exceeded from 31 March to 24 April 2020, with peak activity exceeding the baseline by 46%.[30] Due to a lack of ventilators, HFNO and NIV therapy was widely applied, typically outside the ICU, in overwhelmed healthcare systems such as Wuhan,[36,37] and Italy.[38] This was despite a lack of evidence on their benefits and potentially might have led to delays in intubation.

None of our patients in our case series demised without having been on IMV. HFNO and NIV were also only attempted in the ICU, as opposed to the general ward or high dependency setting. Patients in our case series were either intubated in the emergency department on presentation to the hospital, or intubated in the ICU with no emergent intubations in the general ward setting (Table 2). This was achieved by early referral of deteriorating patients to the ICU. Based on early descriptions of rapid development of ARDS from the onset of dyspnoea,[5] our intensivists practiced a low threshold to admit patients with risk factors of advanced age and medical comorbidities who developed hypoxemia requiring supplemental oxygen for monitoring and early IMV, if required. This was reflected in a high proportion of patients (40.9%) who did not require IMV in our case series. This is in comparison to the higher incidence of IMV in the case series of Lombardy 88%,[28] United Kingdom 72.2%,[29] Scotland 81%,[30] and Atlanta 76%.[31] This practice of early ICU outreach and admission has been shown to be associated with lower mortality in Jiangsu province, China[39] and may have similarly contributed to a lower mortality rate in our patients.

Having sufficient ICU staff was also instrumental in ensuring that all patients received standard ICU care in line with evidence-based guidelines for ARDS and COVID-19. Prone positioning, a labour-intensive intervention, was also applied to more than half of IMV patients and this could not have been done if there was insufficient ICU manpower. Based on small studies conducted outside the ICU,[25,40,41] we had also practised PP on 9 hypoxemic non-intubated patients in the ICU, in case worsening respiratory failure was masked by the short-term improvements in oxygenation, and thus managed to avoid IMV for seven patients. To date, no healthcare worker (HCW) in Singapore contracted COVID-19 in the course of work[42] due to adequate provision of personal protective equipment and segregation of healthcare for non-COVID-19 and COVID-19 patients. Inadequate protection of HCW can significantly widen the health capacity and demand gap by draining hospital staffing and increasing demand for healthcare. In a case series from Wuhan, it was reported that 29% of hospitalised COVID-19 patients were healthcare workers (including 2 from the ICU) who contracted the infection at work.[3]

Study Strengths and Limitations

The major strength of our study is the finding of low COVID-19 mortality with good standard supportive care in the ICU which comprises timely admission, early intubation, lung protective ventilation strategies and careful weaning from IMV. A case series from Hong Kong—a city which enjoyed early success in pandemic mitigation—reported a comparably low ICU mortality rate of 12.5%[43] and underscores the importance of forward planning for ICUs to have sufficient surge capacity in the event of a pandemic. Just like Hong Kong, Singapore has been fortunate to have drawn lessons from its experience with the Severe Acute Respiratory Syndrome and was able to rapidly implement pandemic preparedness drawer plans for its ICUs.[44–46] Our "pandemic ready" ICU was able to achieve mortality rates that were lower than patients with other causes of ARDS[47] by having adequate surge capacity, in turn allowing clinical standards and evidence-based practices to be maintained without resorting to disaster rationing.

Our study is however limited by the small sample size and single-centre experience and therefore the findings may not be generalisable to other patients with severe COVID-19. Secondly, due to data censoring on 30 June 2020, the long-term outcomes of our patients who remain hospitalised are unknown. Thirdly, some patients had missing laboratory tests or missing clinical data.

Conclusion

Our study describes the characteristics and outcomes of COVID-19 patients admitted to a "pandemic ready" ICU in Singapore whilst capacity remains unstressed. Low ICU mortality rates can be achieved with good

accessibility to ICU, early intubation, lung protective ventilatory strategies and good general supportive care in the ICU even if effective anti-viral therapies are not yet widely available. The morbidity of severe COVID-19, however, remains considerable and can rapidly deplete ICU resources in a pandemic. A "pandemic ready" ICU is able to maintain clinical standards and continue evidence-based practices without having to resort to rationing of resources, thereby keeping mortality rates low in the early phase of a pandemic.

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