Clinical course and outcomes of ventilated critically ill COVID-19 patients in Selangor state, Malaysia

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Background: The coronavirus disease 2019 (COVID-19) pandemic has been spreading since December 2019 and still no proven treatment or vaccination has been discovered. Limited case series involving critically ill patients have been reported from South East Asia.

Methods: This is a single center, retrospective case series involving 49 ventilated critically ill COVID-19 patients admitted to Hospital Sungai Buloh, Selangor, Malaysia admitted between 7th March until 16th April 2020. Inclusion criteria are COVID-19 adult patients age more than 12 years old, with history of intubation during their intensive care unit (ICU) stay and admitted between 7th March until 16th April. Data were obtained from electronic health record and ICU progress sheet.

Results: Forty-nine ventilated COVID-19 patients were included {mean 60.2 [standard deviation (SD): 9.3], range: 42–79, male 75.5%}. Most common comorbidities were hypertension 30 (61%), diabetes 26 (53%) and chronic kidney disease (CKD) 8 (16%). Mean PaO_2/FiO_2 (PF) ratio on admission was 115 reflecting severe acute respiratory distress syndrome (ARDS). Fourteen (28.6%) patients required prone ventilation. Patients were intubated for an average of 10 (SD: 8.3) days. All patients received antiviral therapies. The more severely ill patients received either corticosteroid [dexamethasone 11 (22.4%), methylprednisolone 12 (24.5%)] or tocilizumab 8 (16.3%). During their illness, 32 (65.3%) patients developed acute kidney injury (AKI) with 23 (46.9%) patients needing renal replacement therapy (RRT). Average ICU stay is 18 (SD: 10.2) days. Thirty-one patients (57%) managed to be extubated and discharged from ICU while 9 (18.3%) succumbed to death.

Conclusions: The majority of ventilated critically COVID-19 patients survived their ICU stay but often suffered from multiorgan complications.

Keywords: Ventilated; intensive care unit (ICU); coronavirus disease 2019 (COVID-19); Malaysia; outcome; organ failure

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Introduction

Coronavirus disease 2019 (COVID-19) has become a pandemic since it was first reported in December 2019 (1). To date, more than 4 million cases have been detected worldwide affecting over 200 countries with mortality exceeding 200,000 patients (2). Malaysia having had its first case in early January 2020, has seen an exponential increase in cases since then (3).

Our center, originally a designated infectious disease (ID) and trauma center of the Selangor state, has been prepared and dedicated to cater for COVID-19 cases ever since. The Selangor state with its population of 6.3 million, recorded 1,604 cases as of May 10, 2020 (4). This is about a quarter of the total cases recorded in the country (6,665 cases). Our intensive care unit (ICU) is geared up to cater to up to 100 critically ill patients if the need arise. The purpose of this case series is to capture data on management and outcome of ventilated COVID-19 patients in our state.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jeccm-20-82).

Methods

In this observational, descriptive case series, we included 49 adult ventilated patients which were confirmed COVID-19 cases via positive reverse-transcriptase polymerase chain reaction (RT-PCR) assays of specimens collected via nasopharyngeal swabs or tracheal aspirate. These patients were admitted between 7th March 2020 until 16th April 2020. These patients were either intubated in our center following clinical deterioration or transferred from surrounding hospital following a positive COVID-19 RT-PCR results.

All mechanically ventilated adult patients admitted to Hospital Sungai Buloh Intensive Care Unit (HSB ICU) within this period were included. We have excluded patients who fell under patients under investigation (PUI) category, but tested negative for COVID-19. Twenty-six COVID-19 positive non-ventilated patients admitted for close observations while on non-invasive oxygen therapy were also excluded. Patients with missing data from electronic and manual records were excluded.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Malaysian Research and Ethics Committee (MREC) (ID: NMRR-20-2441-54853) and individual consent for this retrospective analysis was waived.

Deidentified patient data were collected from our in hospital electronic-health-information-system (e-His) and ICU nursing charts. Baseline demographics, laboratory values, ventilator days & ICU days were recorded.

Statistical analysis

Data was analyzed using IBM SPSS Statistics 23. Results were reported as means, percentage and counts as appropriate. *T*-tests were used to compare any significant difference between means.

Results

A total of 49 adult patients were included for analysis {mean age, 60 [standard deviation (SD): 9.3]; range, 40–79 years}. The majority are male patients (75%). About 80% of patients had underlying comorbidities, with hypertension being the most common (61.2%) followed by diabetes (53%) and ischemic heart disease (10.2%). A proportion of patient also had pre-existing chronic kidney disease (CKD) (8.1%) and end stage renal failure (ESRF) (8.1%) (*Table 1*).

Baseline laboratory values on admission to ICU showed mean Hb of 13 g/dL (SD: 2), median lymphocyte count of 0.99×10^9/L [interquartile range (IQR): 0.7–1.4], mean white cell count of 9.86×10^9/L (SD: 13.2) and mean platelet count of 234×10^9/L (SD: 99). Median creatinine value was above normal at 125 μmol/L (IQR: 77–195). Total bilirubin mean value was within normal range, however median aspartate transaminase (AST) value was elevated twice (65 unit/L, IQR: 38–104) above the normal range whereas median alanine transaminase (ALT) was normal. Forty-eight patients (98%) had abnormal chest radiographs findings as reported by radiologist. The most common changes were ground glass opacity 79.5%, consolidation 75.5%, interstitial opacity 34.6% and nodular opacity in 8% of patients (*Table 1*).

The average sequential organ failure assessment (SOFA) score on admission to ICU was 6 correlating to a predicted 21.5% mortality. Mean PaO_2/FiO_2 (PF) ratio on admission is 115 (73.4) mmHg reflecting a moderate acute respiratory distress syndrome (ARDS). We observed the tendency for patients to deteriorate clinically between day 4 to 10 of illness thus needing intubation by day 8 (SD: 4.2) of illness. Fourteen patients (28.6%) had to be proned while being mechanically ventilated (*Table 2*).

Table 1 Baseline characteristics of ventilated critically ill COVID-19 patients in Hospital Sungai Buloh

Demographics	N/mean/median	%/SD/IQR	Reference range
Male	37	75.5	
Female	12	24.5	
Age	60.2	9.3	42–79
Comorbids			
Diabetes	26	53.0	
Hypertension	30	61.2	
CKD	8	16.2	
Ischemic heart disease	5	10.2	
No comorbids	10	20.4	
Baseline laboratory values			
Hemoglobin, g/dL	13.0	2.0	13.5–17.4
White blood cell count, ×10^9/L	9.9	13.2	4.078–11.37
Absolute lymphocyte count, ×10^9/L	0.99	0.7–1.4	0.385–1.141
Platelet count, ×10^9/L	228.5	99.3	142–350
Creatinine, µmol/L	100	77–195	62–115
Bilirubin, µmol/L	9.6	6.4–16.3	5–21
ALT, U/L	39.9	30.2–65.3	10–49
AST, U/L	65	38–104	0–34
Chest radiograph findings			
Ground glass opacity	39	79.5	
Consolidation	37	75.5	
Interstitial opacity	17	34.6	
Nodular opacity	4	8.1	

COVID-19, coronavirus disease 2019; SD, standard deviation; IQR, interquartile range; CKD, chronic kidney disease; ALT, alanine transaminase; AST, aspartate transaminase.

The indication for prone ventilation in our institution is PF ratio of 150 or less despite initiation of mechanical ventilation. These patients were having worsening ground glass opacities on serial chest X-ray despite initiation of mechanical ventilation and compassionate antiviral therapy. They were proned between 16–20 hours per session. In the proned group, there was improvement in mean PF ratio after proning of 155. When analyzed using *t*-test the P value is 0.000412 which is statistically significant (P<0.05) (*Table 3*). Patients who have been proned, tend to have higher mean SOFA score on admission and had prolonged mechanical ventilation. However, these differences are not statistically significant (*Table 4*).

All patients received compassionate use of antiviral therapies. The choice of antiviral agents were Lopinavir-Ritonavir 46 (93.8%), Interferon beta-1b 42 (91.3%), Hydroxychloroquine 32 (65.3%), Atazanavir 5 (10.2%) & Ribavirin 3 (6.1%). The selection of antiviral agents were made after joint discussion with ID physicians. Fifteen (30.6%) of patients were given corticosteroid (dexamethasone or methylprednisolone). We also had five patients admitted in the second half of the analysis period who were started on tocilizumab. More than 90% of patients received broad spectrum antibiotics for nosocomial infections throughout their ICU stay (*Table 2*).

A significant number of patients developed organ

Table 2 Clinical parameters of ventilated critically ill COVID-19 patients in Hospital Sungai Buloh

Measures	Mean (SD)/n	Range/%
SOFA score on admission	6.3 (3.22)	2–13
Ventilation		
PF ratio on admission	115 (73.4)	53–305
Day of illness when intubated	8 (4.2)	3–24
Duration of mechanical ventilation (days)	10 (8.3)	2–40
Number of patients requiring prone ventilation (n)	14 (28.6)	
Duration of prone ventilation (hours)	23 (11.7)	10–52
Compassionate drugs use		
Lopinavir-Ritonavir	46	93.8
Interferon beta-1b	42	91.3
Hydroxychloroquine	32	65.3
Atazanavir	5	10.2
Ribavirin	3	6.1
Dexamethasone	11	22.4
Methylprednisolone	12	24.5
Tocilizumab	8	16.3
Organ dysfunction		
AKI	32	65.3
AKI requiring RRT	23	46.9
Pulmonary embolism	4	8.1
Acute liver failure	1	2.0
Myocarditis	1	2.0

COVID-19, coronavirus disease 2019; SD, standard deviation; SOFA, sequential organ failure assessment; PF, PaO_2/FiO_2; AKI, acute kidney injury; RRT, renal replacement therapy.

Table 3 *T*-test comparing mean PF ratio before prone and after prone ventilation

Measures	Before prone		After prone		T-statistic	P value
	Mean	SD	Mean	SD		
PF ratio	103.62	27.60	258.85	116.67	−4.6768	0.000412

PF, PaO_2/FiO_2; SD, standard deviation.

dysfunctions during their clinical course. The most common organ dysfunction was acute kidney injury (AKI) occurring in 32 patients (65.3%). Of this, 23 patients (46.9%) eventually needed dialysis. The latest classification by Acute Kidney Injury Working Group of KDIGO (Kidney Disease: Improving Global Outcome) is used to define AKI (5). Four patients developed pulmonary embolism diagnosed by CT pulmonary angiogram. Acute liver failure occurred in one patient, who eventually succumbed to death. A female patient also developed myocarditis which eventually progressed to fatal cardiogenic shock (*Table 2*).

Our patients were ventilated on average of 11 days.

Table 4 *T*-test to compare the average SOFA score, age and days ventilated between prone and supine group

Measures	Prone		Supine		T-test	P value
	Mean	SD	Mean	SD		
SOFA score	7.00	2.45	6.03	3.48	1.0948	0.2812
Age	58.21	9.83	61.21	9.06	−0.9736	0.3403
Days ventilated	13.07	7.33	9.18	8.48	1.5968	0.1216

SOFA, sequential organ failure assessment; SD, standard deviation.

Table 5 Outcomes of COVID-19 ventilated critically ill patients in Hospital Sungai Buloh

Outcomes	Mean (SD)/n	Range/%
ICU stay (days)	18 (10.2)	4–48
Discharged from ICU	31	57
Death	9	18.3
Ongoing care in ICU	9	18.3

COVID-19, coronavirus disease 2019; SD, standard deviation; ICU, intensive care unit.

Table 6 Outcomes of ventilated COVID-19 patients compared with baselines characteristics

Characteristics	Mean	SD
PF ratio on admission		
Death	83.62	49.03
Still in ICU	110.87	89.72
Discharged from ICU	125.46	76.10
Age		
Death	61.63	8.97
Still in ICU	62.13	7.31
Discharged from ICU	59.19	10.10
SOFA score		
Death	7.50	4.03
Still in ICU	7.38	2.61
Discharged from ICU	5.65	3.08
Number of days ventilated		
Death	18.13	13.26
Still in ICU	8.63	3.50
Discharged from ICU	8.55	4.26

COVID-19, coronavirus disease 2019; SD, standard deviation; PF, PaO_2/FiO_2; ICU, intensive care unit; SOFA, sequential organ failure assessment.

Mean ICU stay was 18 (10.2) days. 30 patients (61%) were managed to be extubated and discharged. Eleven patients are still being managed in ICU. The remaining patients with prolonged ICU stay are either intubated due to prolonged ventilation or awaiting recovery from nosocomial infection. Of those who were extubated but remain in ICU, were the patients with AKI awaiting renal recovery. At the time of writing, we have recorded nine deaths which made up about 18.3% of ventilated patients. Majority of patients died of multiorgan failure complications (*Table 5*).

Patients with worse clinical outcomes i.e., death or prolonged ICU stay, tend to be older, had higher SOFA scores in the first 24 hours of admissions and lower baseline PF ratios (*Table 6*).

Discussion

This case series represented critically ill COVID-19 patients who required mechanical ventilation in our ICU. We also managed non-ventilated patient requiring oxygen therapy with hypoxemic failure or organ failure that needs close monitoring. The latter group of patients benefited from early ICU care and avoid intubation by having close monitoring & meticulous fluid balance. Thus, our ICU workload is more than what has been described.

We have observed a higher incidence of AKI, which is 65% compared to 29% in an observational study by Yang *et al.* in Wuhan (6). Possible factors include a large number of elderly patients with hypertension and undiagnosed CKD who presented late to the hospital. They were among our biggest group of patients who were the most ill needing multiorgan support and had prolonged ICU stay.

Although all our patients received one or more types of antiviral or immunomodulator agents, we could not comment on the efficacy of one over the other agents as we have not had a standard regime and there are many

confounding factors affecting mortality and survival. The selection of antiviral agents were made after joint discussion with ID physicians. Some patients received more than 1 different combinations of antiviral agents. A combination of lopinavir/ritonavir, interferon beta and hydroxychloroquine were initially used. These combinations were later switched to atazanavir and ritonavir. Patients who later developed prolonged QT on electrocardiogram (ECG) or worsening liver enzymes were subsequently withheld from antiviral therapy. The group of patients were started on corticosteroid or immunomodulator were the ones which demonstrated signs and symptoms of cytokine release syndrome (CRS) or sepsis related ARDS based on inflammatory markers and chest X-ray. Again the usage of corticosteroids and tocilizumab were compassionate and patient selection were done by ID physician and intensivists. At present, no drugs have been proven to be safe and effective at treating COVID-19 patients (7).

We practiced early proning for severe ARDS with PF ratio of <150 mmHg together with neuromuscular blockade. Similar rescue strategies has been reported by Yang *et al.* in Wuhan (6). Ten out of 14 of our patients who were ventilated prone managed to be extubated and discharged out of ICU.

The majority of our patients had received broad spectrum antibiotics. The threshold to initiate antibiotics were low especially for patients who were started on corticosteroids or immunomodulators as they were at high risk to develop nosocomial infections. However, most patients were often culture negative. Other co-factors that put patients at risk of cross infection include limited nursing care especially on viral filters change and endotracheal tube suctioning and presence of indwelling catheters. The initiation of antimicrobial agents was as suggested by the Society of Critical Care Medicine (SCCM) through their Surviving Sepsis Campaign COVID-19 Guidelines but with de-escalation and daily evaluation of treatment duration (8).

Our fatality rate of 18.3% out of the ventilated patients is currently lower than reported by Richardson *et al.* The latter reported 24.5% death among ventilated patients in New York City area (9). The initial mortality rate among ventilated critically ill in Hubei Province in China was even higher at between 81–97% (10). Our lower mortality rate might be as a results of early ICU admission and early intubation policy. Malaysia currently implementing a policy of admitting positive COVID-19 patients either to a low risk quarantine center or hospital if they exhibit symptoms. In wards, patients who needed higher oxygen requirement

of more than 3 L/min will be referred for ICU care. Thus, we were able avoid catastrophic hypoxic arrest that might go unnoticed in wards. Patients who required more than 8 L/min of non-rebreather mask will be electively intubated as we did not practice applying non-invasive ventilation (NIV) for newly diagnosed COVID-19 patients.

Limitations of this study includes being in a single center within a state. However, as the state of Selangor recorded the highest number of cases, it did reflect the severity of cases in Malaysia's worst affected region. Second, is the absence of post discharge follow up to determine patient outcome following ICU discharge.

Conclusions

This case series reflected the clinical management and outcome of ventilated critically ill COVID-19 patients in the Selangor state of Malaysia. Although the fight against COVID-19 is far from over, we have seen a plateauing of cases due to movement control order that has been ongoing nationwide. Until definite treatment or vaccination is found, we were hoping that the numbers of severe cases can be controlled and that those critically ill, can be better managed on supportive treatments.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jeccm-20-82

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appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Malaysian Research and Ethics Committee (MREC) (ID: NMRR-20-2441-54853) and individual consent for this retrospective analysis was waived.

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