Outcomes and evolving clinical practice in COVID-19 patients admitted to ICU in Montreal, Quebec, Canada – A retrospective cohort study

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Abstract

Background: The COVID-19 pandemic is responsible for millions of infections worldwide and a significant proportion of these patients will be admitted to the intensive care unit. Limited data is available to describe this critically ill population. We describe the characteristics, outcomes and the evolution in management of critically ill Canadian patients with COVID-19 at a single designated pandemic centre in Montreal, Canada.

Methods: A retrospective cohort study was performed on all consecutive critically ill COVID-19 patients admitted between March 5th and May 21st, 2020. We also analyzed how clinical practice and outcomes evolved over time.

Results: A total of 106 patients were included in this study. The ICU mortality was 16.0% with 75.5% of patients discharged from the ICU. Mortality in patients requiring mechanical ventilation was 16.9%. Prone positioning was used in 27.4% of patients and no patient was placed on ECMO. Acute kidney injury was the most common complication, seen in 18.9% of patients, and 11.3% of patients required renal replacement therapy. 50.0% of patients received corticosteroids. As our practice evolved, there was a significant decrease in incidence of intubation (83.3% vs 50.0%, $p<0.01$), and the use of high-flow nasal cannula increased (4.2% vs 44.0%, $p<0.01$) with a trend towards improved mortality.

Interpretation: Our cohort of critically ill COVID-19 patients has a lower mortality than previously described in other jurisdictions. Access to critical beds and liberal use of corticosteroids may have contributed to our low observed mortality.

Introduction

Coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in December 2019, and has caused millions of infections and claimed over 350,000 lives with an overall mortality rate of approximately 3% and a mortality of up to 60% in the critically ill.[1-5] Limited information is available to describe the outcomes of patients admitted to Intensive Care Units (ICU) in Canada. The Jewish General Hospital was the first designated pandemic centre for adults in Montreal, the epicentre of COVID-19 in Canada. As of May 27th, 2020, it had admitted 17% of all COVID-19 ICU patients in the city.[6] We describe the outcomes and patient management of critically ill Canadian patients with COVID-19 at our institution.

Methods

Context

This study was conducted at the Jewish General Hospital (JGH) in Montreal, Quebec, Canada, a 637 bed university–affiliated tertiary-care adult hospital which was designated by the provincial government as the initial receiving centre for all adult COVID-19 patients in Montreal during the first wave of pandemic admissions. The JGH ICU is a mixed medical/surgical unit with a maximum baseline capacity of 26 patients. To respond to the pandemic, a plan to gradually increase the number of available ICU beds to 50 was implemented. The first positive case of SARS-CoV-2 in the province of Quebec was diagnosed on February 27th, 2020. The JGH admitted Quebec's first COVID-19 patient to the ICU on March 5th.

During the following three months, many changes occurred in our institution and in the province. All elective surgeries were cancelled at our hospital on March 16th, and by the second week of March, the Quebec government declared a province-wide state of emergency. Quarantine and social distancing measures were initiated, generalized closures were implemented, and by the third week of March, only essential services were kept open. Due to the surge of patients in our ICU, on March 21st, the province expanded the list of designated hospitals in the Montreal region that could admit patients with COVID-19.

Staffing in the JGH ICU consisted of critical care trained attending physicians, critical care residents, as well as other trainees. As the ICU census expanded, as of March 28th critical care and anesthesia attendings provided in-house coverage 24 hours/day. Resident physician, ICU nursing and respiratory therapy capacity was increased by redeployment from other areas of the hospital, which allowed nursing to patient ratios to be maintained at a maximum of 1:1.2. All patients were cared for in single rooms and all health care workers in the unit had access to personal protective equipment (PPE).

As per our initial COVID-19 institutional protocol, between March 5th and April 24th, all patients were prescribed azithromycin 500mg daily for 5 days and hydroxychloroquine 200mg PO TID for 10 days. All ICU patients were treated with standard weight based thromboprophylaxis with low molecular weight heparin, or unfractionated heparin, if contraindicated. However, intermediate dosing was permitted at the discretion of the treating physician.

Management of mechanical ventilation was at the discretion of the treating physician. In our ICU, pressure regulated volume control was the default mode used for most patients with acute respiratory distress syndrome (ARDS), with a ventilation goal of 6 ml/kg predicted body weight (PBW). Fraction of inspired oxygen (FiO_2) titration for intubated patients was supported using either the ALVEOLI low or high PEEP table, depending on the patient's oxygen needs and response to initial PEEP titration.[7] Prone positioning was often initiated when the FiO_2 was sustained above levels that are generally considered to be safe. Prone positioning was also utilized in non-intubated patients on high-flow nasal cannula (HFNC). Neuromuscular blockade was used when required to maintain patient ventilator synchrony and plateau pressures less than 30 cm H_2O, after maximizing sedation and opioids. The use of non-invasive mask ventilation was not approved for use in patients with COVID-19 during the study period and our institution does not provide HFNC outside of the ICU.

Analysis

A retrospective chart review was performed on all consecutive patients with polymerase chain reaction (PCR) positive SARS-CoV-2, admitted to the ICU with COVID-19, between March 5th and May 21st, with follow up data available until June 5th, 2020.

Data was collected by authors SD, SY, and JL and abstracted from chart review and laboratory and pharmacology electronic medical records. Collected variables included demographic information, comorbidities, initial vital signs, laboratory results and COVID-19 specific symptoms and epidemiology. Interventions, including medical therapies, oxygenation methods and ventilation strategies, were collected for all patients. Clinical outcomes, including length of stay, morbidity and mortality, were also analyzed.

Baseline characteristics were described using descriptive statistics. Continuous variables were reported using median and interquartile range (IQR). Assuming a nonparametric distribution, Mann-Whitney U test was used to analyze differences for continuous variables and χ^2 test was used to describe categorical variables, as appropriate. As international data emerged on COVID-19 and we gained local experience as a high-volume pandemic centre, our clinical practice evolved. To evaluate this change over time, we compared, a priori, outcomes of patients admitted in the early phase of the pandemic (March 6th to April 5th) with those admitted later (April 6th to May 21st). For the purposes of this analysis, we elected to exclude the patients who had a no intubation advance directive. A Kaplan-Meier curve analysis was performed to examine the difference between the early versus late groups, with respect to the number of patients discharged alive from ICU over time. A logrank test was used to analyze differences between these two time periods. All tests were two-sided with a significance defined as $p<0.05$. All analyses were performed using SAS version 9.4 and STATA version 15.

This study was approved by the local Research Ethics Board of *Centre Intégré Universitaire en Santé et Services Sociaux* (CIUSSS) West-Central Montreal, Jewish General Hospital.

Results

During the study period, we admitted a total of 106 patients to the ICU with COVID-19 pneumonia, representing 23% of all COVID-19 hospitalizations in our institution. 76 (71.7%)

were directly admitted from the emergency department. Four SARS-CoV-2 positive patients admitted for other medical/surgical reasons were excluded from our analysis. Table 1 presents the patient demographics and baseline clinical and laboratory characteristics of the patients. Median age was 66 years (IQR 54-74) with 64 male patients (60.4%). Eight patients (7.6%) were not candidates for intubation based on advanced directives. The median Charlson comorbidity index was 3 (IQR 1-4) and the median sequential organ failure assessment (SOFA) score on admission was 5 (IQR 3-8).

Sixty-five patients (61.3%) required endotracheal intubation, with 29 patients (27.4%) undergoing prone positioning and 24 patients (22.6%) requiring neuromuscular blockade. HFNC was used for 48 patients (45.3%). No patients required extracorporeal membrane oxygenation (ECMO). The most frequently prescribed medical therapies were azithromycin (88.7%), hydroxychloroquine (70.8%), broad-spectrum antibiotics (67.0%), and corticosteroids (50.0%). The most common corticosteroid used was dexamethasone (61.3%) (Table 2).

Our ICU mortality was 16.0% and hospital mortality was 17.9%, with 75.5% and 64.2% of the cohort discharged from ICU and hospital, respectively. Hospital mortality fell to 12.2% when excluding patients who refused intubation. No patients below the age of 50 died and only two of 80 patients who were discharged alive from ICU died on the medical ward (Figure 1).

ICU mortality in patients requiring mechanical ventilation was 16.9%, with the majority of ventilated patients being older than 60 years old (Figure 2). Median duration of ventilation was 11 days (IQR 8-16), with 38.5% of patients requiring mechanical ventilation for more than 14 days.

Median ICU and hospital length of stay were 9 (IQR 3-16) and 16 (IQR 8-23) days, respectively. The most common complication was acute kidney injury (18.9%) while thromboembolic events occurred in 14.2% of patients (Table 3).

We compared patient management and outcomes between our early and late time periods. Baseline patient characteristics were similar except for age, with the second time period having slightly younger patients than the first (67 vs 62 years, $p<0.01$) (Table 4). There was a significant decrease in the number of patients intubated (83.3% vs 50.0%, $p<0.01$) and there was a trend towards using lower PEEP (incidence of high PEEP use: 40.0% vs 24.0%, $p=0.19$). Later patients were also significantly more likely to be supported by HFNC (excluding use post-extubation) (4.2% vs 44.0%, $p<0.01$). Of the patients on HFNC, 42.7% never required intubation. The proportion of patients discharged alive from ICU was similar in both groups despite later patients having a shorter study period (Figure 3). Overall, there was a non-significant decrease in hospital mortality (16.7% vs 8.0%, $p=0.19$).

Significantly more corticosteroids were used in the later group (39.6% vs 62.0%, $p=0.03$), while ICU acquired infections significantly decreased (35.4% vs 10.0%, $p<0.01$). There was also a trend towards a shorter stay in ICU (12 vs 7 days, $p=0.14$).

Interpretation

In our retrospective cohort study of critically ill COVID-19 patients, we described an ICU mortality of 16.0%. Despite comparable baseline characteristics, our cohort has a significantly lower mortality rate compared to China, Europe and the United States.[2,3,8,9]

Our management practices evolved as we gained clinical experience and new data emerged. We avoided the use of HFNC on COVID-19 patients in the early period because of the theoretical risk of increased aerosolization and initial paucity of data on how SARS-CoV-2 is transmitted.[10,11] However, as literature emerged showing minimal associated risk to health care workers, we began treating patients with HFNC.[12] All patients on HFNC were treated in negative pressure rooms with standard PPE and KN95 masks. Importantly, only three health care workers in the ICU tested positive for SARS-CoV-2 during the study period, all of whom had an alternative higher risk exposure outside of the ICU.

Although we did not demonstrate a significant mortality difference between our two time periods, overall intubations were reduced, with a significant proportion of the patients on HFNC never requiring intubation, which is consistent with literature in respiratory failure in patients without COVID-19.[13] We were also able to extubate earlier and transition to HFNC rather than prolong the duration of invasive mechanical ventilation, which may have contributed to the significantly shorter ICU length of stay found in the later time period.

With the recognition of COVID-19 specific clinical phenotypes, we used less PEEP and neuromuscular blockade over time, and we also noted a decreased incidence of acute kidney injury and need for renal replacement therapy.[14] High incidences of renal failure requiring dialysis have been reported in other cohorts, with some centres preparing for use of acute continuous ambulatory peritoneal dialysis as traditional modes of renal replacement became overwhelmed.[15] While this may reflect a direct effect from the virus itself, it is possible that avoiding the known adverse hemodynamic effects of positive pressure ventilation and high PEEP, and blunting the inflammatory cascade with corticosteroids could account for the lower incidence seen in the later phase of our cohort.[16-18] Further research accounting for other confounding variables would be required to explore this hypothesis.

A large proportion of our patients received corticosteroids in the context of cytokine release syndrome (CRS) or severe ARDS. Corticosteroids were given late (median 13 days) after the start of symptoms, and the majority of patients were prescribed a regimen of dexamethasone as described by Villar *et al.*[19] In addition, 10.4% of patients were treated with Tocilizumab for CRS. Corticosteroid use for coronavirus associated respiratory failure and CRS remains controversial, however a short course of corticosteroids given after the peak of viral shedding may be warranted, as the risk of worsening infection and outcome appears low.[20-25] Although the overall mortality rate is similar to the results from another Canadian study,[26] it is possible that treatment with corticosteroids and/or Tocilizumab was responsible for the shorter duration of mechanical ventilation that we observed. We look forward to the results of the recently completed Recovery trial from the United Kingdom, with early results showing low dose dexamethasone improves mortality in severe COVID-19.

At the outset, we administered hydroxychloroquine to all patients based on preliminary reports of efficacy,[27] however this was subsequently discontinued on April 24th following emergence of data showing lack of benefit and ongoing questions of safety.[28,29] Although no patient died from a malignant arrhythmia, it remains possible patients may have experienced other drug side effects, including delirium or drug-drug interactions.

Using HFNC, standard lung protective ventilation, frequent use of prone positioning and corticosteroids, there were no patients who met local criteria for ECMO. Although it remains possible that some patients could have benefited from early ECMO use, current reports suggest a very high mortality associated with the use of ECMO in COVID-19. Moreover, rational use of such a resource intensive therapy is critical in the context of a pandemic.[30-32]

During the study period, although local capacity was at times under stress, ICU resources were never completely overwhelmed, which may have contributed to our relatively low ICU mortality. Redeployment of nursing and respiratory therapists from other areas of the hospital to increase ICU capacity was critical as the JGH ICU admitted the majority of critically ill COVID-19 patients in the first few weeks of the Quebec pandemic. This proportion decreased to eventually stabilize at 10% of all provincial COVID-19 ICU admissions as other ICUs in Montreal were activated by the provincial pandemic protocol (Figure 4).

Another possible contributor to the lower mortality observed in both our study and that of Mitra et al. is the free universal health care system in Canada which minimizes socio-economic barriers to access care.[26] Reports from the USA show high rates of death in marginalized populations and in particular, African Americans.[33,34] In contrast, we found no mortality association with race, with only one death out of 16 Black Canadian patients.

This study has several important limitations. Given the retrospective nature of our study, any link between our interventions and the observed outcomes is speculative. The duration of follow-up is limited, although only a small proportion of patients remain in the ICU at the time of censoring. It is also a single centre study in Canada which may not be applicable to other jurisdictions, however, this remains the largest case series of critically ill patients in the epicentre of the Canadian COVID-19 pandemic.

Conclusion

The mortality of critically ill patients with COVID-19 in the Canadian context is significant, however appears to be less than previously described in other countries. Provincial and institutional pandemic preparedness and the ability to quickly increase human resources may be in part responsible for the lower observed mortality. High quality studies are urgently needed to help guide the appropriate use of mechanical ventilation strategies, including the role of HFNC and prone positioning, as well as antiviral, corticosteroids and/or antithrombotic therapy in COVID-19.

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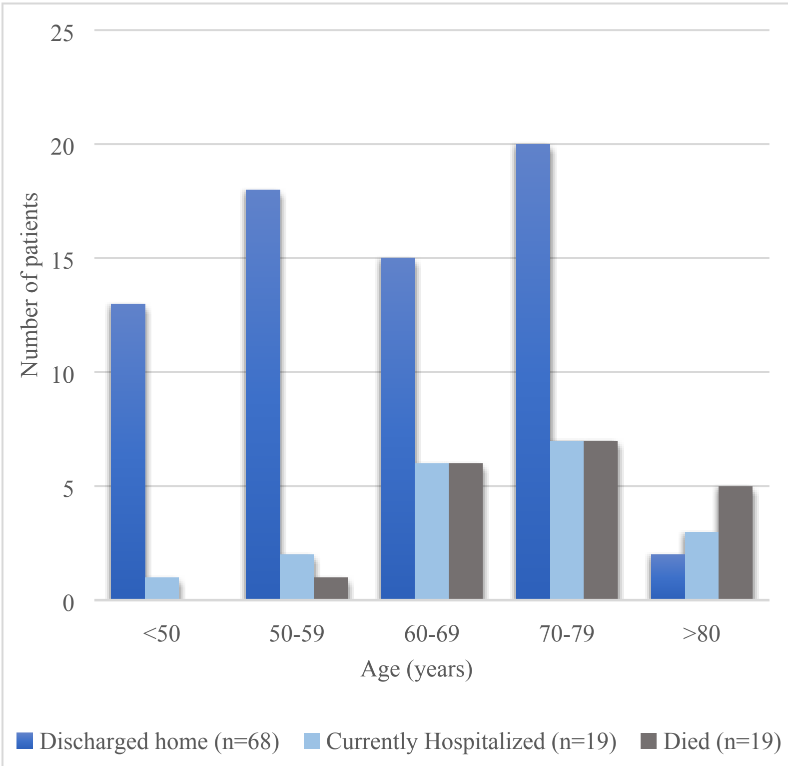

Figure 1. Disposition by age.

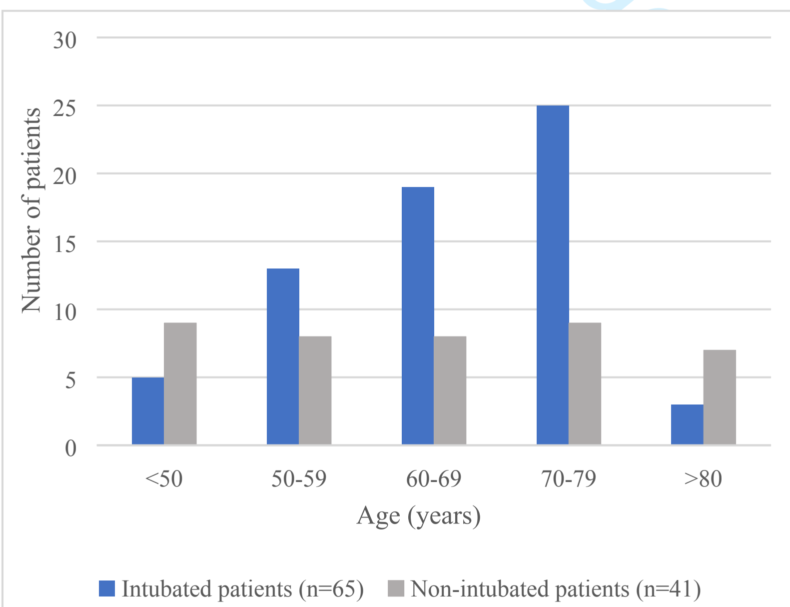

Figure 2. Intubation status by age

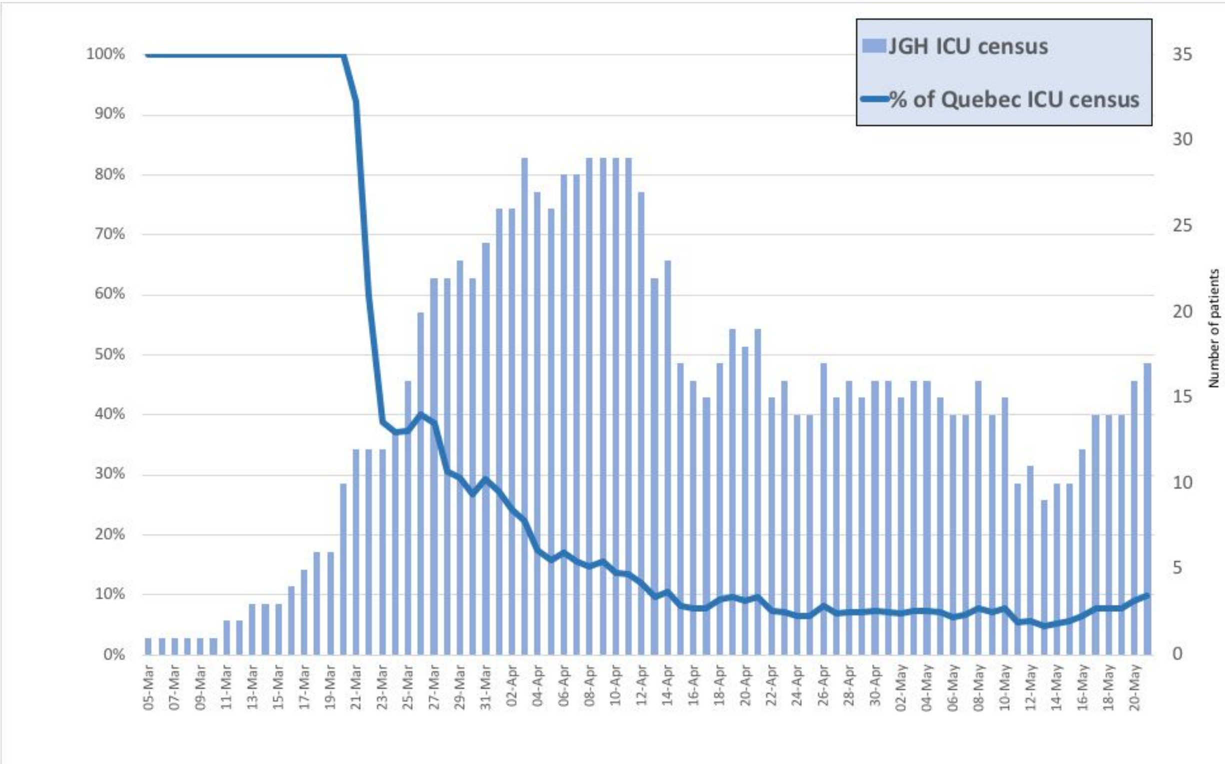

Figure 3. Daily COVID-19 census

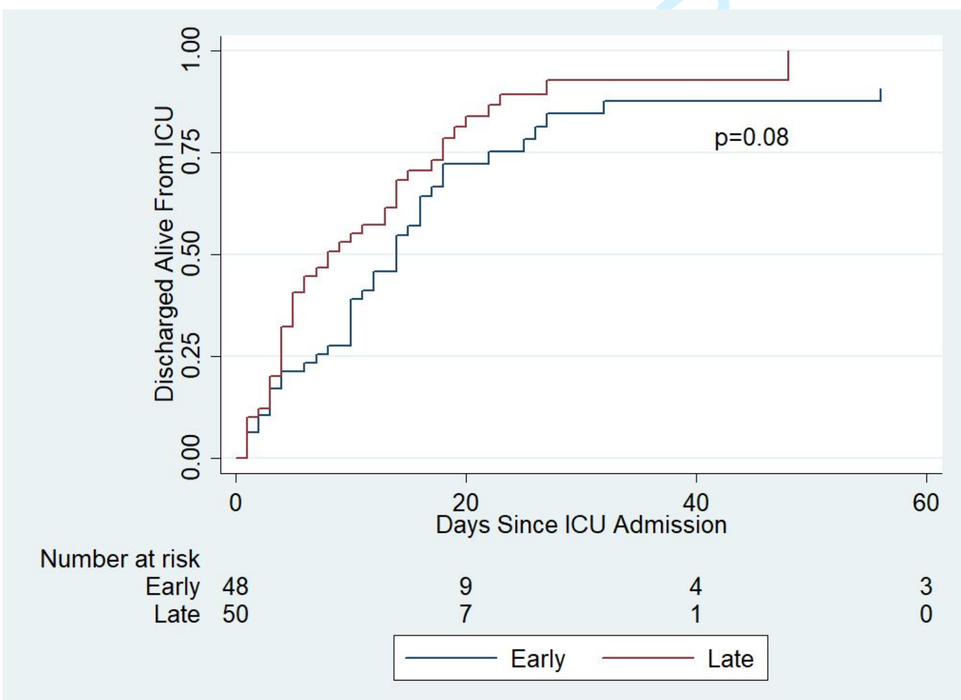

Figure 4: Kaplan-Meier survival to ICU discharge by time period

Characteristics	Total n=106
Age, median (IQR)	66 (54-74)
Male	64 (60.4)
Body mass index, median (IQR), n=76	29.4 (25.3-33.8)
Pregnant	3 (2.8)
Black Canadian	16 (15.1)
Symptomatic household contact	34 (32.1)
Patients with a no intubation advanced directive	8 (7.6)
Nursing home resident	11 (10.4)
Charlson comorbidity index, median (IQR)	3 (1-4)
SOFA score*, median (IQR)	5 (3-8)
PaO_2/FiO_2†, n=63	133 (95-174)
Comorbidities	
Hypertension	55 (51.9)
Diabetes mellitus	30 (28.3)
Coronary artery disease	15 (14.2)
Obesity, n=89	41 (46.1)
Chronic kidney disease	10 (9.4)
Chronic obstructive lung disease	8 (7.6)
Asthma	10 (9.4)
Malignancy	10 (9.4)
Immunocompromised‡	12 (11.3)

Table 1. Baseline demographics and clinical characteristics
Results expressed as n (%) unless otherwise stated.
*SOFA: Sequential organ assessment score excluding the neurologic component; Worst SOFA calculated after 24hrs of admission.
†Worst PaO_2/FiO_2 calculated 24hrs post intubation.
‡HIV or patient treated with steroid, chemotherapy, or biologic medication.

Intervention	Total n=106
Respiratory management	
Invasive mechanical ventilation	65 (61.3)
High PEEP†	22 (33.9)
PEEP at 24 hours post intubation, median (IQR), n=63	10 (8-12)
Prone positioning	29 (27.4)
Intubated	19 (65.5)
Not intubated	10 (34.5)
High-flow nasal cannula	48 (45.3)
Initial respiratory support‡	29 (60.4)
Post-extubation support	21 (43.8)
Medication	
Neuromuscular blockade	24 (22.6)
Corticosteroids	53 (50.0)
Symptom onset to receipt of steroids, days, median (IQR)	13 (10-17)
Azithromycin	94 (88.7)
Hydroxychloroquine	75 (70.8)
Tocilizumab	11 (10.4)
Oseltamivir	8 (7.6)
Lopinavir/Ritonavir	6 (5.7)

Table 2. Critical care management of ICU patients with COVID-19
Results expressed as n (%) unless otherwise stated. PEEP: positive end-expiratory pressure
†High PEEP defined as PEEP > 15 cm H_2O during mechanical ventilation
‡ Two patients had high-flow nasal cannula for both indications

	Total n=106
Outcomes	
Hospital mortality	19 (17.9)
ICU mortality	17 (16.0)
ICU mortality in mechanically ventilated patients, n=65	11 (16.9)
Discharged from hospital	68 (64.2)
Discharged alive from ICU	80 (75.5)
Currently in ICU	7 (6.6)
Currently on medical ward	12 (11.3)
Duration of mechanical ventilation, days, median (IQR), n=57	11 (8-16)
ICU length of stay, days, median (IQR), n=99	9 (3-16)
Hospital length of stay, days, median (IQR), n=87	16 (8-23)
Tracheostomy	6 (5.7)
Complications	
ICU acquired infection*	22 (20.8)
Atrial fibrillation	24 (22.6)
Acute kidney injury†	20 (18.9)
Renal replacement therapy	12 (11.3)
Thrombotic events‡	15 (14.2)
Pulmonary embolism / Deep vein thrombosis	11 (10.4)
Ischemic stroke	6 (5.7)
Peripheral arterial thrombosis	1 (0.9)

Table 3. Outcomes and complications in critically ill COVID-19 patients.
Results expressed as n (%) unless otherwise stated.
*Positive culture results with pathogenic organisms
†Greater than 2x baseline creatinine
‡thromboembolic event confirmed by imaging, two patients had > 1 thrombotic events.

	Early † N=48	Late‡ N=50	p-value

Age, median (IQR)	67 (62-74)	62 (50-72)	0.01
Male	32 (66.7)	28 (56.0)	0.28
Comorbidities*			0.52
0	15 (31.3)	21 (42.0)	
1	17 (35.4)	16 (32.0)	
≥2	16 (33.3)	13 (26.0)	
PaO_2/FiO_2 ratio††, n=63	136 (112-177)	114 (83-161)	0.01
Management			
High PEEP (>15 cm H_2O), n (%)	16 (40.0)	6 (24.0)	0.19
Prone positioning, n (%)	12 (25.0)	16 (32.0)	0.44
Not intubated	1	8	0.28
High-flow nasal cannula, n (%)	15 (31.3)	28 (56.0)	0.01
Initial respiratory support	2 (4.2)	22 (44.0)	<0.01
Neuromuscular blockade, n (%)	16 (33.3)	8 (16.0)	0.05
Hydroxychloroquine	48 (100.0)	25 (50.0)	<0.01
Corticosteroids, n (%)	19 (39.6)	31 (62.0)	0.03
Symptom onset to receipt of steroids, days, median (IQR), n=50	17 (13-22)	12 (9-15)	0.02
Outcomes			
Intubation, n (%)	40 (83.3)	25 (50.0)	<0.01
Hospital mortality, n (%)	8 (16.7)	4 (8.0)	0.19
ICU mortality, n (%)	7 (14.6)	4 (8.0)	0.30
Discharged from hospital, n (%)	33 (68.8)	35 (70.0)	0.89
Discharged alive from ICU	37 (77.1)	43 (86.0)	0.25
Duration of mechanical ventilation, days, median (IQR), n=57	11 (8-17)	12 (6-14)	0.87
ICU length of stay, days, median (IQR), n=92	12 (6-17)	7 (4-14)	0.14
Hospital length of stay, days, median (IQR), n=80	17 (11-24)	14 (8-23)	0.23
Complications			
ICU acquired infection, n (%)	17 (35.4)	5 (10.0)	<0.01
Acute kidney injury, n (%)	12 (25.0)	8 (16.0)	0.27
Renal replacement therapy, n (%)	9 (18.8)	3 (6.0)	0.05

Table 4. Patient characteristics, management and outcomes by time period.
† Early: Patients admitted between March 5th and April 5th, 2020;
‡ Late: Patients admitted between April 6th and May 21st, 2020.
*Comorbidities include: hypertension, diabetes mellitus, coronary artery disease, and chronic kidney disease.
††Worst PaO_2/FiO_2 calculated 24hrs post intubation.