Early experience with critically ill patients with COVID-19 in Montreal

Expériences initiales avec les patients atteints de la COVID-19 en état critique à Montréal

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Abstract

Purpose *Montreal has been the epicentre of the coronavirus disease (COVID-19) pandemic in Canada. Given the regional disparities in incidence and mortality in the general population, we aimed to describe local characteristics, treatments, and outcomes of critically ill COVID-19 patients in Montreal.*

Methods *A single-centre retrospective cohort of consecutive adult patients admitted to the intensive care unit (ICU) of Hôpital du Sacré-Coeur de Montréal with confirmed COVID-19 were included.*

Results *Between 20 March and 13 May 2020, 75 patients were admitted, with a median [interquartile range (IQR)] age of 62 [53–72] yr and high rates of obesity (47%), hypertension (67%), and diabetes (37%). Healthcare-*

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related infections were responsible for 35% of cases. The median [IQR] day 1 sequential organ failure assessment score was 6 [3–7]. Invasive mechanical ventilation (IMV) was used in 57% of patients for a median [IQR] of 11 [5–22] days. Patients receiving IMV were characterized by a moderately decreased median [IQR] partial pressure of oxygen:fraction of inspired oxygen (day 1 PaO_2:F_iO_2 = 177 [138–276]; day 10 = 173 [147–227]) and compliance (day 1 = 48 [38–58] mL/cmH$_2$O; day 10 = 34 [28–42] mL/cmH$_2$O) and very elevated estimated dead space fraction (day 1 = 0.60 [0.53–0.67]; day 10 = 0.72 [0.69–0.79]). Overall hospital mortality was 25%, and 21% in the IMV patients. Mortality was 82% in patients ≥ 80 yr old.

Conclusions *Characteristics and outcomes of critically ill patients with COVID-19 in Montreal were similar to those reported in the existing literature. We found an increased physiologic dead space, supporting the hypothesis that pulmonary vascular injury may be central to COVID-19-induced lung damage.*

Résumé

Objectif *Montréal a été l'épicentre de la pandémie du coronavirus (COVID-19) au Canada. Étant donné les disparités régionales dans l'incidence et la mortalité dans la population générale, nous avons tenté de décrire les caractéristiques locales, les traitements et le devenir des patients atteints de la COVID-19 en état critique à Montréal.*

Méthode *Notre étude de cohorte rétrospective monocentrique a inclus tous les patients adultes admis consécutivement à l'unité de soins intensifs de l'Hôpital du Sacré-Cœur de Montréal avec un diagnostic confirmé de COVID-19.*

Résultats *Soixante-quinze patients ont été admis entre le 20 mars et le 13 mai 2020. Ceux-ci avaient un âge médian [écart interquartile (ÉIQ)] de 62 [53–72] ans et présentaient une incidence élevée d'obésité (47 %), d'hypertension (67 %) et de diabète (37 %). Les transmissions associées aux soins de santé étaient responsables de 35 % des cas. Au jour 1, le score SOFA (Sequential Organ Failure Assessment – évaluation séquentielle de défaillance des organes) médian [ÉIQ] était de 6 [3–7]. La ventilation mécanique invasive (VMI) a été utilisée chez 57 % des patients, pour une durée médiane [ÉIQ] de 11 [5–22] jours. Les patients ayant reçu une VMI étaient caractérisés par une médiane [ÉIQ] modérément réduite de la pression partielle de la fraction d'oxygène inspiré (jour 1 PaO_2:F_iO_2 = 177 [138–276]; jour 10 = 173 [147–227]), de la compliance (jour 1 = 48 [38–58] mL/cmH$_2$O; jour 10 = 34 [28–42] mL/cmH$_2$O), ainsi que par une fraction d'espace mort estimé très élevée (jour 1 = 0,60 [0,53-0,67]; jour 10 = 0,72 [0,69-0,79]). La mortalité hospitalière était de 25 % globalement, et de 21 % chez les patients avec VMI. La mortalité a atteint 82 % chez les patients âgés de ≥ 80 ans.*

Conclusion *Les caractéristiques et le devenir des patients en état critique atteints de la COVID-19 à Montréal étaient semblables à ceux rapportés dans la littérature existante. Nous avons observé un espace mort physiologique augmenté, ce qui appuie l'hypothèse que des lésions vasculaires pulmonaires seraient primordiales dans les lésions pulmonaires induites par la COVID-19.*

The first case of coronavirus disease (COVID-19) was described in Wuhan, China, in late 2019,[1] with subsequent global spread. In Canada, the Montreal metropolitan area has become the principal epicentre, and this influx of severe cases has put significant stress on local hospitals and intensive care units (ICUs).[2] The catchment area of our hospital has been particularly affected with more than 7,000 confirmed cases of COVID-19.[3] A rate of 3,083 confirmed cases/100,000 population was reached in one of the covered boroughs,[4] the highest reported rate in the country and similar to that reported in New York City.[5]

Severe acute respiratory syndrome coronavirus 2 infection can result in a wide range of clinical manifestations, ranging from asymptomatic to critically ill.[6] Exaggerated inflammatory mediator release triggered by the cytopathic viral infection and coagulation dysregulation are thought to be central to the development of severe lung damage.[7] Different distribution of determinants of this host response may significantly impact the expression of the disease in different populations. Older populations with higher rates of hypertension, diabetes, and obesity have a higher risk of more severe disease.[8] Extrinsic factors, including healthcare system characteristics (i.e., number of hospital or ICU beds), may also impact patient management and disease progression towards severe forms. Finally, cultural differences in terms of goals of care and end-of-life decision-making may also affect ICU admission and choice of supportive therapy.[9]

Given regional differences in the above-mentioned factors, detailed characterization of critically ill patients is needed to understand how COVID-19 affects our population. Our aim was to describe the demographics, presentation, treatments, and outcomes of a cohort of critically ill adult patients with COVID-19 hospitalized in a large academic ICU in Montreal, Canada.

Figure Age group distribution and hospital mortality rate
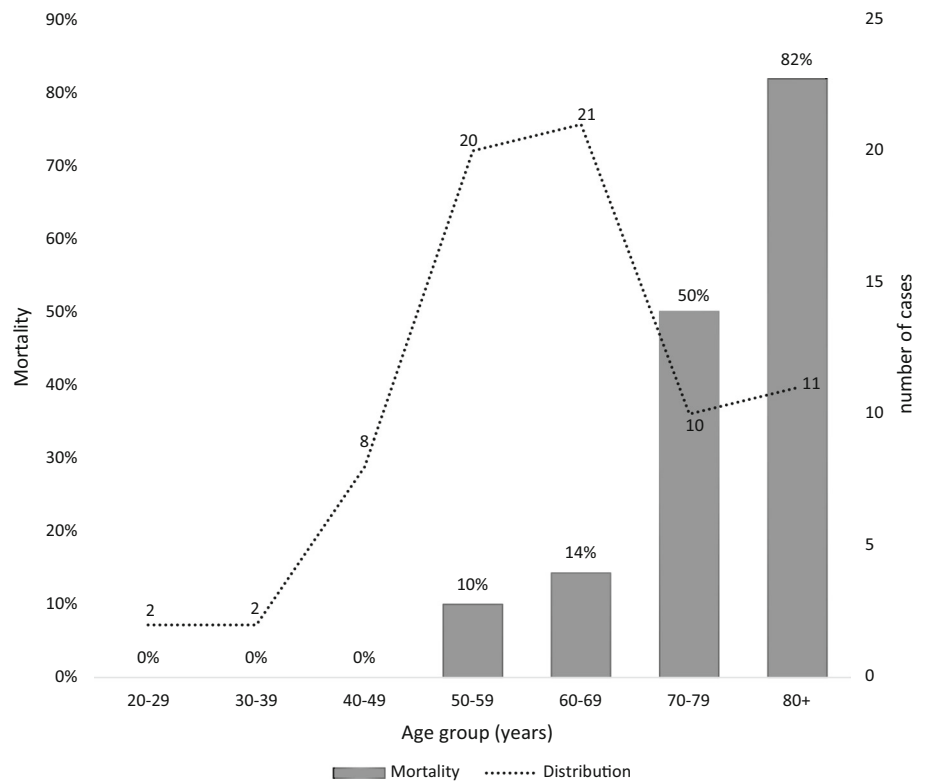
Methods

Study design

We conducted a single-centre retrospective observational study of consecutive adult patients with confirmed COVID-19 admitted to the ICU of Hôpital du Sacré-Coeur de Montréal between 20 March and 13 May 2020. Diagnosis was established in all cases by reverse transcriptase-polymerase chain reaction in nasopharyngeal, tracheal aspirate, or bronchoalveolar lavage specimens. The institutional review board approved the study and waived the requirement for informed consent.

Setting

Hôpital du Sacré-Coeur de Montréal is a large academic hospital with a pre-pandemic 38-bed capacity mixed medical-surgical ICU and a 1:1.3 nurse to patient ratio. It is a level-1 trauma centre and severe acute respiratory failure centre, with extracorporeal membrane oxygenation (ECMO) capacity. Hôpital du Sacré-Coeur de Montréal was among the first designated COVID-19 centres in the province. An organizational plan was in place to progressively increase the number of ICU beds to > 100 in a stepwise approach if needed.[10] All COVID-19 cases were managed by board-certified intensivists supported by a multidisciplinary team

according to international treatment guidelines, including lung-protective ventilation, prone position, neuromuscular blockade, and conservative fluid management.[11,12] Intensive care unit admission criteria for COVID-19 patients included an oxygen requirement of > 5 L·min^{-1} accompanied with signs of respiratory distress. Patients with pre-established limitations of care excluding invasive mechanical ventilation (IMV) and cardiopulmonary resuscitation (CPR) were only admitted if considered for a trial of high-flow oxygen therapy or non-invasive positive-pressure ventilation (NIPPV). These therapies were permitted only in negative-pressure ICU rooms and their use was initially strongly discouraged because of aerosol generation. Some patients admitted from the emergency department (ED) did not have pre-established goals of care (GOC). Such patients were admitted quickly in an effort to liberate ED beds and GOC were discussed in the ICU. In patients with respiratory distress, NIPPV was sometimes started to provide time to discuss GOC. Although GOC were continuously reviewed as per patient evolution and families' wishes, only initial GOC at ICU admission were used for analysis.

An early intubation strategy was initially advocated, with a slightly longer period of observation before intubation as experience was gained. With a few exceptions, no antimalarial, antiviral, or immunomodulating agents were administered outside of clinical trials. Corticosteroids were used at the discretion of

Table 1 Baseline characteristics (n = 75)

Variable	Value n (%) or median [IQR]	Variable	Value n (%) or median [IQR]
Demographics		CKD	11 (15)
Sex (male)	50 (67)	Malignant neoplasm	7 (9)
Age	62 [53–72]	*Drug use prior to admission*	
BMI	29.1 [25–32.1]	ACEi	9 (13)
Weight category		ARB	12 (17)
Normal weight (BMI < 25)	17 (29)	NSAID	2 (3)
Overweight (BMI 25–30)	17 (29)	*Laboratory parameters at ICU admission*	
Obese (BMI > 30)	24 (41)	WBC ($10^9 \cdot L^{-1}$)	7.9 [6–11.4]
Ethnic group		Lymphocytes ($10^9 \cdot L^{-1}$)	0.9 [0.6–1.3]
Caucasian	38 (51)	CRP ($mg \cdot L^{-1}$)	136 [71–192]
African and Caribbean	16 (21)	LDH ($U \cdot L^{-1}$)	379 [296–575]
Latin American	7 (9)	AST ($U \cdot L^{-1}$)	51 [33–66]
Asian	6 (8)	ALT ($U \cdot L^{-1}$)	35 [24–56]
Other/unknown	8 (11)	Fibrinogen ($g \cdot L^{-1}$)	6.46 [5.48–7.53]
Healthcare-related	26 (35)	D-dimers ($ng \cdot mL^{-1}$)	1262 [721–2432]
Inpatient acquisition	17 (23)	Ferritin ($\mu g \cdot L^{-1}$)	1389 [436–1825]
Healthcare worker	9 (12)	hs-Troponin I ($ng \cdot L^{-1}$)	20 [6–72]
Past medical history		*ICU day 1 severity of illness*	
No past medical history	11 (15)	SOFA respiratory	3 [1–3]
Hypertension	50 (67)	SOFA coagulation	0 [0–0]
Chronic cardiac condition	18 (24)	SOFA liver	0 [0–0]
Diabetes	27 (37)	SOFA cardiovascular	3 [0–3]
Smoking	4 (6)	SOFA central nervous system	0 [0–0]
Asthma	8 (11)	SOFA renal	0 [0–1]
COPD	5 (7)	Total SOFA score	5 [3–7]
Other chronic pulm. dis.	10 (14)	*Duration of symptoms (days) at ICU admission*	8 [6–11]
Immunosuppression	4 (5)		

ACEi = angiotensive coverting enzyme inhibitor; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ARB = angiotensive receptor blockers; AST = aspartate aminotransferase; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive lung disease; CRP = C-reactive protein; hs = high sensitivity; ICU = intensive care unit; LDH = lactate dehydrogenase; NSAID = non-steroidal anti-inflammatory drugs; pulm. dis. = pulmonary disease; SOFA = sequential organ failure assessment; WBC = white blood cell count

treating physicians; as were doses and agents used for thromboprophylaxis and anticoagulation. Thromboprophylaxis and anticoagulation were individualized according to estimated risk of thrombosis and bleeding. There was no systematic venous thromboembolism (VTE) screening. Investigation was performed according to treating physician's clinical suspicion.

Data collection and analysis

We recorded baseline characteristics, laboratory parameters, ICU day 1 sequential organ failure assessment (SOFA) score,[13] treatments, and outcomes. Day 1 of IMV arterial blood gas values and IMV parameters were collected (those closest to 6:00 AM). Data were extracted from our ICU database (SEMi Criticare®, Montreal, QC, Canada), complemented by retrospective chart review. The ventilatory ratio, estimated dead space fraction (V_d:V_t; Weir rearrangement using the Harris–Benedict equation for the resting energy expenditure), and mechanical power (simplified) were calculated according to published formulas.[14–16] Descriptive statistics were used to summarize clinical data. Categorical variables were presented as counts and percentages and continuous variables as median [interquartile range (IQR)]. In patients missing PaO_2 measurements, we used the SpO_2:F_iO_2 ratio to calculate the respiratory component of the SOFA score.[17] Missing data imputation was not performed. Data were analyzed

using IBM SPSS Statistics, Version 25.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline characteristics

Between 20 March and 13 May 2020, 357 patients with confirmed COVID-19 diagnosis were hospitalized, 75 of which were admitted to the ICU (21%). The median [IQR] age of ICU patients was 62 [53–72] yr (Figure and Table 1). A high proportion of patients were overweight or obese (24/58; 70%) and had a past medical history of hypertension (50/75; 67%), diabetes mellitus (27/75; 37%), and chronic cardiac conditions (18/75; 24%). The median [IQR] duration of symptoms at admission was 8 [6–11] days. Lymphopenia (defined as absolute count < $1.0*10^9 \cdot L^{-1}$) was present in 78% of patients. Most patients exhibited a hyperinflammatory profile, with elevated C-reactive protein (median [IQR] 136 [71–192] $mg \cdot L^{-1}$) and ferritin (median [IQR] 1,389 [436–1,825] $\mu g \cdot L^{-1}$), and abnormal liver function test results ($n = 48$; 64%). Twenty-six patients probably acquired COVID-19 infection in a healthcare facility (35%): 17 as patients (23%) and nine as healthcare workers (HCW) (12%). The median [IQR] ICU day 1 SOFA score was 5 [3–7]. The most frequent organ failures (organ score $\geq$ 1) were respiratory (66/74; 89%), cardiovascular (40/74; 54%), and renal (23/74; 31%). No data were missing for age, sex, past medical history, and past drug use. Body mass index was missing in 34% of patients, day 1 laboratory parameters globally in 17% of patients, and SOFA components in 2% of patients (Table 2).

Pharmacologic therapy

A significant proportion of patients (43/75; 57%) received therapeutic anticoagulation and corticosteroids (35/75; 47%). The highest daily prescribed steroid dose ranged from 25 to 2,500 mg of hydrocortisone equivalent. The median [IQR] was 400 [200–600] mg. Reasons for steroid administration were sometimes multiple and could not be clearly established from patient records in all cases. They included acute respiratory distress syndrome, severe bronchospasm, upper airway edema, and vasopressor-dependent sepsis.

Non-invasive respiratory support

A high-flow nasal cannula was used in only two patients (3%) because of concerns over aerosolization. Non-invasive positive-pressure ventilation was also initially avoided, but as the pandemic evolved, it was used more frequently (16/75; 21%), mainly in patients with respiratory distress who declined IMV (10/16; 63%). Failure of NIPPV was high in that context (seven deaths/10; 70%). In the remaining six patients that consented to IMV, NIPPV was used as the initial support modality in two patients likely to have poor outcomes with IMV (advanced chronic pulmonary diseases); intubation was successfully avoided in both. In the other four patients, NIPPV was used post-extubation; it failed in three of those four instances (one patient who declined re-intubation died and two patients were re-intubated).

Invasive mechanical ventilation

A total of 43 patients underwent IMV (57%). On day 1 of IMV, the median [IQR] partial pressure of oxygen:fraction of inspired oxygen ($PaO_2:F_iO_2$) ratio was 177 [138–276]. Patients were initially characterized by relatively preserved respiratory system compliance (C_{RS}) (median [IQR] 48 [38–58] mL/cmH$_2$O), high $V_d:V_t$ (median [IQR] 60 [53–67]%), and high ventilatory ratio (median [IQR] 1.74 [1.32–2.11]) (Table 3). Continuous infusions of neuromuscular blockers were used in 16 of the IMV patients (38%), nitric oxide in 15 patients (36%), prone position in 11 patients (26%), and ECMO in one patient (2%). The median [IQR] duration of IMV was 11 [5–22] days overall, 13 [5–24] days in survivors, and 10 [7–13] days in non-survivors. Ten patients underwent percutaneous tracheostomies (24% of IMV patients).

Outcomes

Overall, 14 patients (19%) were diagnosed with VTE while in the ICU: eight with pulmonary embolism and six with deep vein thrombosis (Table 4). Patients had a median [IQR] of 18 [2–28] days free of IMV at 28 days. The median [IQR] ICU and hospital length of stays (LOS) were 10 [4–19] days and 17 [10–42] days, respectively. At the time of extracting the data (27 July 2020), no patient was still in the ICU and only one patient was still hospitalized for reasons unrelated to COVID-19. The ICU mortality was 23% (17/75) and hospital mortality 25% (19/75). Age group distribution and mortality are detailed in the Figure. Only two patients below 60 yr of age died (2/32; 6%). Fifteen of the 19 patients who died (79%) gave do-not-resuscitate orders upon ICU admission. The mortality was 67% (8/12) for patients with initial GOC excluding both resuscitation and IMV, 54% (7/13) for patients with initial GOC excluding resuscitation but allowing IMV, and 8% (4/49) for those with initial full-code status. There were no missing data on ICU therapies and outcomes.

Table 2 Received Treatments in the ICU (*n* = 75)

Therapy	*n* (%)
Anti-infective agents	
Oseltamivir	3 (4)
Antibacterial	71 (95)
Antimalarial	4 (5)
Antifungal	12 (16)
Antithrombotic agents	
Initial dosing	
Thromboprophylaxis	52 (69)
Intermediate	3 (4)
Therapeutic anticoagulation	20 (27)
Maximal dosing	
Thromboprophylaxis	31 (41)
Intermediate	1 (1)
Therapeutic anticoagulation	43 (57)
Reason for anticoagulation	
Empirical	5 (12)
Cardiac indication	16 (37)
VTE	14 (33)
CRRT / ECMO	4 (9)
Antiplatelet therapy use	20 (27)
Immunomodulating agents	
Corticosteroids	35 (47)
Other	0 (0)
Non-pharmacological	
Invasive mechanical ventilation	42 (56)
Non-invasive positive-pressure ventilation	16 (21)
High-flow nasal cannula	2 (3)
Extracorporeal membrane oxygenation	1 (1)
Continuous renal replacement therapy	7 (9)
IMV-specific support	
NMB: bolus only	6/43 (14)
NMB: continuous infusion	16/43 (37)
Nitric oxide	15/43 (35)
Prone position	11/43 (26)
Percutaneous tracheostomy	10/43 (23)

CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; NMB = neuromuscular blockers; VTE = venous thromboembolism, IMV = invasive mechanical ventilation

Subgroups

Patients were categorized into three groups (Table 5). Group A consisted of patients agreeing to IMV but did not receive it (*n* = 20). This group was younger and had fewer comorbidities. They presented with the lowest rate of lymphopenia, the lowest ferritin, and lowest D-dimers, while having the highest median C-reactive protein levels. All but one patient survived and the ICU LOS was short (median [IQR], 3.7 [3.0–7.8] days). Group B included patients with more severe disease that were treated with IMV (*n* = 43). Mortality in this group was 19%, and the ICU LOS was longer (median [IQR], 12.5 [9.8–28.2] days). Group C patients or their substitute decision-makers expressed the desire not to undergo IMV after discussion with treating physicians (*n* = 13). This group with limitations of care was the oldest and had the most comorbidities. A greater proportion had lymphopenia (92%); and they had the highest median [IQR] ferritin (1,562 [1,632–3,060]) and D-dimers (2,273 [1,632–3,060]). The majority were treated with NIPPV (10/13; 77%). Mortality in this group was 69%.

Discussion

In this first account of critically ill COVID-19 patients treated in the Canadian epicentre of the pandemic, we have found encouraging outcomes despite facing one of the largest numbers of cases per capita. We observed a high proportion of overweight and obese patients with hypertension and diabetes, as previously described.[18] Patients typically presented to the ICU more than a week after symptom onset with lymphopenia, a hyperinflammatory profile, and evidence of coagulation activation. Of concern, nosocomial transmission was responsible for more than a third of cases. Invasive mechanical ventilation was used in 57% of patients. These were characterized by moderately low $PaO_2:F_IO_2$ and compliance and very elevated estimated dead space fraction and ventilatory ratio. Hospital mortality was 25% overall and 21% in IMV patients. Critically ill patients with limitations of care excluding IMV had a high non-invasive ventilation failure rate (70%) and a high mortality rate (69%). Finally, patients ≥ 80 yr old had an 82% mortality rate.

As of 21 July, 6,268 HCW had been infected in Montreal, representing 22% of COVID-19 cases in the city.[4] No official figures on nosocomial transmission have been published by provincial authorities, with scarce data worldwide. Early records from China reported that only 3.8% of COVID-19 patients were HCW,[6] while in Italy they represented 12% of total cases[19] and 10–20% of hospitalized COVID-19 patients in the UK.[20] Inpatients who acquire COVID-19 during hospitalization are already ill and may be more likely to require ICU. Our observations, in conjunction with the strong representation of HCW among COVID-19 cases reported by public health authorities, may suggest that nosocomial transmission acted as a major amplifier in our region despite strict adherence to national guidelines for infection prevention. Documented in-hospital clusters of infection

Table 3 Invasive mechanical ventilation parameters during the first two weeks ($n = 43$)

Parameters	Day 1	Day 3	Day 7	Day 10	Day 14
Number of ventilated patients	43	38	29	24	19
Ventilation mode					
Volume assist/control	32 (74)	16 (42)	13 (45)	11 (46)	5 (26)
Pressure support	11 (26)	22 (58)	13 (45)	12 (50)	10 (53)
Other	0	0	3 (10)	1 (4)	4 (21)
Tidal volume (Vt) (mL)	500 [460–585]	500 [450–600]	500 [450–600]	500 [450–540]	506 [450–610]
V_t (mL)·kg^{-1} of PBW	7.5 [6.8–8.7]	7.6 [6.7–8.8]	7.5 [6.6–8.8]	7.5 [6.9–8.4]	7.1 [5.8–8.4]
Respiratory rate (breaths·min^{-1})	20 [16–22]	22 [20–28]	24 [20–28]	25 [21–28]	24 [17–28]
Plateau pressure (cmH$_2$O)*	21 [19–24]	26 [24–28]	25 [22–27]	26 [20–28]	30 [28–32]
PEEP (cmH$_2$O)	9 [8–10]	8 [5–10]	10 [8–12]	8 [7–11]	8 [7–10]
Driving pressure (cmH$_2$O)*	13 [10–16]	14 [12–16]	15 [12–15]	14 [12–16]	17 [15–24]
Pressure support (cmH$_2$O)	13 [9–13]	13 [9–15]	16 [14–20]	13 [10–17]	13 [10–15]
$P_{0.1}$	1.0 [0.7–2.6]	2.5 [1.5–3.6]	2.5 [1.1–3.8]	3.1 [2.0–3.9]	3.0 [2.0–4.2]
F_IO_2	50 [40–65]	50 [40–60]	50 [35–65]	50 [40–58]	45 [33–53]
pH	7.38 [7.35–7.42]	7.40 [7.37–7.42]	7.4 [7.31–7.45]	7.41 [7.36–7.43]	7.41 [7.38–7.45]
PaCO$_2$ (mmHg)	44 [40–49]	49 [44–57]	55 [48–67]	57 [46–61]	50 [43–65]
PaO$_2$ (mmHg)	91 [75–111]	85 [72–99]	80 [69–95]	89 [75–99]	86 [75–99]
HCO$_3$ (mmol·L^{-1})	25 [23–28]	29 [25–32]	33 [28–38]	32 [28–35]	32 [30–35]
PaO$_2$:F$_I$O$_2$	177 [138–276]	184 [140–245]	159 [120–237]	173 [147–227]	208 [162–250]
Compliance (C$_{RS}$) (mL/cmH$_2$O)*	48 [38–58]	41 [31–52]	49 [37–63]	34 [28–42]	32 [18–35]
Estimated physiologic V$_d$:V$_t$	0.60 [0.53–0.67]	0.70 [0.59–0.75]	0.74 [0.72–0.78]	0.72 [0.69–0.79]	0.72 [0.64–0.78]
Ventilatory ratio	1.74 [1.32–2.11]	2.21 [1.65–2.91]	2.54 [2.25–3.02]	2.38 [2.06–3.11]	2.34 [1.86–2.88]
Mechanical power (J·min^{-1})*	20.3 [16.2–27.8]	27.8 [24.6–39.2]	26.95 [20.8–37.0]	26.28 [21.0–40.4]	38.2 [28.4–40.2]

Data provided as n (%) or median [interquartile range]. HCO$_3$ = bicarbonate; PBW = predicted body weight; PEEP = positive end expiratory pressure; PaCO$_2$ = arterial partial pressure of carbon dioxide; PaO$_2$:F$_I$O$_2$ = partial pressure of oxygen:fraction of inspired oxygen; $P_{0.1}$ = negative pressure measured 100 msec after the initiation of an inspiratory effort; V$_t$ = tidal volume; V$_d$:V$_t$ = dead space fraction. *Only reported for patients on volume assist control ventilation mode

did initially occur in our institution, originating from non-isolated asymptomatic patients in whom COVID-19 was not suspected. In response, we modified our infection control policies to consider all inpatients as suspected COVID-19 cases, and these new measures sharply reduced nosocomial transmission.

With 166 deaths per 100,000 inhabitants, the COVID-19-related mortality in the Montreal metropolitan area is among the highest reported.[4] Nevertheless, nursing ratios were preserved throughout the crisis and no triage was needed. A centralized dispatch centre helped distribute cases more evenly between designated hospitals. Importantly, the vast majority of individuals who died were never transferred to hospital wards or ICUs, as 64% of deaths in the province occurred in nursing homes.[3] Nursing-home physicians made substantial efforts to discuss GOC at the crisis onset. This spared hospital resources as no nursing-home patient was admitted to our ICU. Avoidance of IMV in group C patients may have prevented lengthy ICU stays. A shared decision-making model[21] with prompt recognition of patients with poor prognosis by clinicians and realistic patient and family expectations may have considerably preserved resources. Resources could then be allocated fully to those who would benefit the most, perhaps contributing to the relatively low mortality seen in patients with a full-code status. Nevertheless, caution is warranted in the interpretation of the association between GOC and outcomes as there is a potential self-fulfilling prophecy.

The hospital mortality rate observed in our cohort was similar to that reported in a recent meta-analysis of international cohorts of critically ill patients (26%),[22] but higher than in a recent cohort from Vancouver (15%).[23] One of the main limitations of these comparisons is that baseline patient characteristics and extrinsic factors may strongly influence the observed mortality rates. While group B patients are cared for in the ICU in most settings, some group A and C patients could be treated in high-dependency units outside of the ICU in some hospitals. In our institution, resources from our high-dependency units were merged with those of our ICU to adapt more easily to sudden increases in demand for negative-pressure rooms.

Table 4 Patient outcomes

Outcome	Value
Venous thromboembolism (all)	14 (19)
DVT	6 (8)
PE	8 (11)
Pneumothorax or pneumomediastinum	7 (9)
Durations	
Ventilator-free days	18 [2–28]
Duration of IMV, days	11 [5–22]
ICU length of stay, days	10 [4–19]
Hospital length of stay, days	17 [10–42]
ICU status	
Still in ICU*	0
Survived to ICU discharge	58 (77)
Deceased	17 (23)
Hospital status	
Still in hospital	1 (1)
Survived to hospital discharge	55 (73)
Deceased	19 (25)

Data provided as *n* (%) or median [interquartile range]

DVT = deep vein thrombosis; ICU = intensive care unit; IMV = invasive mechanical ventilation; PE = pulmonary embolism

*At manuscript submission

Hospital characteristics and intensity of ICU-bed demand greatly influence the relative composition of patients in a given ICU, with significant impact on overall mortality. Restricting comparisons between cohorts to patients that underwent IMV (group B) may circumvent this limitation.[9]

Interestingly, the mortality observed in IMV patients (21%) was similar to that described in cohorts from Boston (17%), New York (25%), and Vancouver (20%), and lower than that in Lombardy (35%), Germany (53%), and China (97%).[18,23–27] Differential follow-up may explain some of the differences. The mortality may be underestimated in cohorts with a significant number of patients still in the ICU at the time of reporting, which was not the case in our study. As the indications and timing of initiation of IMV may vary significantly,[9] we could also compare different patients. Nevertheless, baseline physiologic indices of severity seem to suggest otherwise. PaO_2:F_IO_2 ratios were similar across cohorts: 182 in Boston, 160 in Lombardy, 180 in Vancouver, and 177 in our cohort.[23–25] Our cohort had a higher C_{RS} (48 mL/cmH$_2$O) than reported in Boston (35 mL/cmH$_2$O) and Vancouver (35 mL/cmH$_2$O).[23,24] Nevertheless, C_{RS} was not associated with survival in a recent unadjusted retrospective analysis of a cohort of COVID-19 patients.[28] Moreover, we found a higher V_d:V_t (60% *vs* 45%) and ventilatory ratio (1.74 *vs* 1.25) than in Boston,[24] indicators that have previously been shown to predict worst outcomes in patients with acute respiratory distress syndrome.[14,16]

We suspect that the high V_d:V_t and ventilatory ratio may be caused by alveolar capillary microthrombi, as seen in autopsy specimens.[29] The high rate of VTE we report (19%), despite a high rate of therapeutic anticoagulation (27% to 57%), supports a prothrombotic state. Moreover, signs of widespread capillary angiopathy were recently shown on computed tomography (CT) pulmonary angiography and dual-energy CT in patients with severe COVID-19.[30] The increased dead space, in conjunction with the hyperinflammatory profile with repeated febrile episodes, resulted in the persistent need for high minute ventilation in a significant proportion of IMV patients. This manifested as relentless air hunger whenever neuromuscular blockers and sedation were weaned, as illustrated by the relatively high $P_{0.1}$ despite high opiate doses in patients on IMV for more than a week. When patients were re-sedated, potentially injurious high-intensity IMV (mechanical power >17 J·min^{-1})[31] had to be applied to maintain acid-base balance, even with bicarbonate infusions. The high ventilatory requirement potentially resulted in a vicious cycle of ventilator or self-inflicted lung injury promoting further lung damage, which in turn increased ventilatory intensity. This is nicely illustrated by the slowly increasing plateau and driving pressures and steep increases in mechanical power with decreasing C_{RS} over time. Our group was conservative with ECMO use because of the relatively good response of hypoxemia to prone positioning and inhaled nitric oxide. One wonders, however, if ECMO could have broken this vicious cycle if instituted early in selected patients with high ventilatory intensity, even with easily managed hypoxemia.

Our study has limitations. The single-centre design limited the sample size and prohibited inferential statistics. All cases of morbidity and mortality may not have been captured as only in-hospital outcomes were assessed. Strengths of our study include it being the first subgroup analysis of patients according to their GOC, shedding light on the excellent prognosis of patients with full-code status. Moreover, no patients were still in the ICU upon data extraction, compared with 56% overall in previous cohorts presenting outcomes of critically ill patients.[22] This draws a much more accurate picture of clinical outcomes.

Conclusion

We found that characteristics and outcomes of critically ill patients with COVID-19 in Montreal were similar to those reported in the existing literature. Some findings did stand out. A significant proportion of ICU patients likely

Table 5 Characteristics and outcomes of patient subgroups

Variable	Group A	Group B	Group C
Definition	Consent to IMV, IMV not used	Consent to IMV, IMV used	Decline IMV, IMV not used
n	19	43	13
Age	56 [46–67]	60 [54–67]	81 [70–83]
No medical history	6 (32)	5 (12)	0
Hypertension	8 (42)	30 (70)	12 (92)
Diabetes mellitus	6 (32)	15 (35)	6 (50)
Lymphopenia ($<1.0\cdot10^9\cdot L^{-1}$)	14 (78)	32 (74)	12 (92)
Ferritin ($g\cdot L^{-1}$)	787 [371–2364]	1406 [420–1681]	1562 [482–2929]
CRP ($mg\cdot L^{-1}$)	177 [151–193]	123 [62–236]	114 [79–165]
D-dimers ($ng\cdot mL^{-1}$)	1125 [873–2151]	1088 [599–2329]	2273 [1632–3060]
Day 1 SOFA score	2 [0–4]	6 [5–7]	8 [4–8]
VTE	2 (11)	12 (28)	0
VFDs	28 [28–28]	11 [0–22]	6 [2–28]
ICU LOS (days)	3.7 [3.0–7.8]	12.5 [9.8–28.2]	3.9 [2.0–10.1]
ICU mortality	0 (0)	8 (19)	9 (69)
Hospital mortality	1 (5)	9 (21)	9 (69)

Data presented as *n* (%) or median [interquartile range]

CRP = C-reactive protein; ICU = intensive care unit; IMV = invasive mechanical ventilation; LOS = length of stay; SOFA = sequential organ failure assessment; VFDs = ventilator-free days; VTE = venous thromboembolism

acquired the virus in healthcare facilities, highlighting the importance of appropriate infection control policies. Non-invasive positive-pressure ventilation had a high failure rate (70%) when used in critically ill patients with limitations of care excluding IMV. Finally, we found a significantly increased physiologic dead space in patients on IMV, supporting the hypothesis that pulmonary vascular injury may be at the heart of COVID-19-induced lung damage.

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