

ORIGINAL



Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study

COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators*

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Abstract

Purpose: To describe acute respiratory distress syndrome (ARDS) severity, ventilation management, and the outcomes of ICU patients with laboratory-confirmed COVID-19 and to determine risk factors of 90-day mortality post-ICU admission.

Methods: COVID-ICU is a multi-center, prospective cohort study conducted in 138 hospitals in France, Belgium, and Switzerland. Demographic, clinical, respiratory support, adjunctive interventions, ICU length-of-stay, and survival data were collected.

Results: From February 25 to May 4, 2020, 4643 patients (median [IQR] age 63 [54–71] years and SAPS II 37 [28–50]) were admitted in ICU, with day-90 post-ICU admission status available for 4244. On ICU admission, standard oxygen therapy, high-flow oxygen, and non-invasive ventilation were applied to 29%, 19%, and 6% patients, respectively. 2635 (63%) patients were intubated during the first 24 h whereas overall 3376 (80%) received invasive mechanical ventilation (MV) at one point during their ICU stay. Median (IQR) positive end-expiratory and plateau pressures were 12 (10–14) cmH₂O, and 24 (21–27) cmH₂O, respectively. The mechanical power transmitted by the MV to the lung was 26.5 (18.6–34.9) J/min. Paralyzing agents and prone position were applied to 88% and 70% of patients intubated at Day-1, respectively. Pulmonary embolism and ventilator-associated pneumonia were diagnosed in 207 (9%) and 1209 (58%) of these patients. On day 90, 1298/4244 (31%) patients had died. Among patients who received invasive or non-invasive ventilation on the day of ICU admission, day-90 mortality increased with the severity of ARDS at ICU admission (30%, 34%, and 50% for mild, moderate, and severe ARDS, respectively) and decreased from 42 to 25% over the study period. Early independent predictors of 90-day mortality were older age, immunosuppression, severe obesity, diabetes, higher renal and cardiovascular SOFA score components, lower PaO₂/FiO₂ ratio and a shorter time between first symptoms and ICU admission.

Conclusion: Among more than 4000 critically ill patients with COVID-19 admitted to our ICUs, 90-day mortality was 31% and decreased from 42 to 25% over the study period. Mortality was higher in older, diabetic, obese and severe ARDS patients.

Keywords: Acute respiratory distress syndrome, Mechanical ventilation, COVID-19, Outcome, Mortality risk factor

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Management and Writing Committee and COVID-ICU Investigators are listed in "Acknowledgement" section.

Introduction

From March to May 2020, Europe was massively affected by the coronavirus disease 2019 (COVID-19) outbreak. In that context, the REVA network [1] designed a specific registry (COVID-ICU), to prospectively collect characteristics, management, and outcomes of patients admitted to intensive care units (ICUs) for severe COVID-19 in France, Belgium, and Switzerland. In France, as of October 1st, 2020, 395,104 patients had been tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 32,365 deaths have been associated with the disease. On April 8, 2020, the number of COVID-19 patients hospitalized in French ICUs peaked at 7148.

A few case-series [2–5] have described baseline characteristics and short-term mortality (up to 28-days after ICU admission) ranging from 26 to more than 50% in critically ill patients with COVID-19. However, recovery from severe COVID-19 often takes several weeks and a substantial number of these patients were still in the ICU or the hospital at the time their outcome was evaluated [4, 5]. Notably, 28-day mortality was 41% in the control care group of the RECOVERY trial, which showed that dexamethasone improved the survival of patients receiving invasive mechanical ventilation or oxygen at randomization [6].

The present study reports data of 4244 patients with laboratory-confirmed SARS-CoV-2 infection admitted to the ICU and for whom day-90 status was available. We also evaluated risk factors associated with 90-day mortality in these critically ill patients.

Methods

Study Design, Patients

COVID-ICU is a multi-center, prospective cohort study conducted in 149 ICUs from 138 centers, across three countries (France, Switzerland, and Belgium). Centers were invited to participate by public announcements and by the Réseau Européen de recherche en Ventilation Artificielle (REVA) network (70 centers were active members of this network). We included in the present report data from participating ICUs that had enrolled at least one patient with complete data on age and 90-day vital status. COVID-ICU received approval from the ethical committee of the French Intensive Care Society (CESRLF 20–23) in accordance with our local regulations. All patients or close relatives were informed that their data were included in the COVID-ICU cohort.

All consecutive patients over 16 years of age admitted to the participating ICU between February 25, 2020, and May 4, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Take-home message

In this cohort study that included 4244 adult patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection admitted to the ICU, 80% received invasive mechanical ventilation. Mortality 90 days after ICU admission was 31% in the whole cohort and 37% in the subgroup of patients who received invasive mechanical ventilation on the day of ICU admission. Among these patients with early intubation, mortality increased with the severity of ARDS at ICU admission (30%, 34%, and 50% for mild, moderate, and severe ARDS, respectively).

infection were included. Laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay from either nasal or pharyngeal swabs, or lower respiratory tract aspirates [7]. Patients without laboratory-confirmed COVID-19 were not included, even if they presented with a typical radiological pattern.

Inclusions were stopped on May 4, 2020, after enrollment of 4643 patients admitted to the ICU. Survival status up to 90 days after ICU admission was obtained for 4244 of them.

Data collection

Day 1 was defined as the first day when the patient was in ICU at 10 am. Each day, the study investigators completed a standardized electronic case report form. Baseline information collected at ICU admission were: age, sex, body mass index (BMI), active smoking, Simplified Acute Physiology Score (SAPS) II score [8], Sequential Organ Failure Assessment (SOFA) [9], comorbidities, immunodeficiency (if present), clinical frailty scale [10], date of the first symptom, dates of the hospital and ICU admissions. The case report form prompted investigators to provide a daily-expanded data set including respiratory support devices (oxygen mask, high flow nasal cannula, or non-invasive ventilation), mechanical ventilation settings (positive end-expiratory pressure (PEEP), the fraction of inspired oxygen (FiO_2), respiratory rate, tidal volume, plateau pressure, arterial blood gas, standard laboratory parameters, and adjuvant therapies for acute respiratory distress syndrome (ARDS) such as the use of continuous neuromuscular blockers, nitric oxide, prone position, corticosteroids, or extracorporeal membrane oxygenation until day-90. Driving pressure was defined as plateau pressure minus PEEP and mechanical power (J/min) was calculated as follows: Mechanical power (J/min) = $0.098 \times \text{tidal volume} \times \text{respiratory rate} \times (\text{peak pressure} - 1/2 \times \text{driving pressure})$ [11]. If not specified, peak pressure was considered equal to plateau pressure. Ventilatory ratio was defined

as (minute ventilation \times PaCO₂) – (predicted body-weight \times 100 \times 37.5) [12].

ARDS severity, complications, and outcomes

ARDS was graded based on the Berlin definition for patients undergoing mechanical ventilation (invasive or non-invasive) on ICU day 1 [13]. Patients on nasal, mask or high-flow oxygen therapy were not included in this group. However, their day-1 PaO₂/FiO₂ was calculated by converting O₂ flow to estimated FiO₂ (see conversion tables in the supplement) [14]. ICU-complications and organ dysfunction included acute kidney failure requiring renal replacement therapy, thromboembolic complications (distal venous thrombosis or proven pulmonary embolism by either pulmonary CT angiography or cardiac echography), ventilator-associated pneumonia, and cardiac arrest. Clinical suspicion of ventilator-associated pneumonia was confirmed before antibiotics either by quantitative distal bronchoalveolar lavage cultures growing $\geq 10^4$ cfu/mL, blind protected specimen brush distal growing $\geq 10^3$ cfu/mL, or endotracheal aspirates growing $\geq 10^6$ cfu/mL.

Patient outcomes included the date of liberation from mechanical ventilation, dates of ICU and hospital discharge, vital status at ICU and hospital discharge, and 28, 60, and 90 days after ICU admission.

Statistical analyses

Characteristics of patients were described as frequencies and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables. Categorical variables were compared by Chi-square or Fisher's exact test, and continuous variables were compared by Student's *t* test or Wilcoxon's rank-sum test. Kaplan–Meier overall survival curves until Day 90 were computed, and were compared using log-rank tests. The median length of stay in ICU and in hospital were also estimated using a Kaplan–Meier estimator to take into account patients that may be still in ICU at the time of the analysis.

Baseline risk factors of death at Day 90 were assessed within the whole cohort using univariate and multivariate cox regression. Baseline variables (i.e., obtained during the first 24 h in the ICU) included in the multivariate model were defined a priori, and no variable selection was performed (see the description of the statistical analysis plan in the Supplement). ICU admission dates were split into four calendar periods (i.e., before March, 15; from March 16 to 31; from April 1 to 15; and after April 16). Proportional hazard assumption was assessed by inspecting the scaled Schoenfeld residuals and Harrell's test [15] (Table S4). Multiple imputations were used to

replace missing values when appropriate (Figure S1–S2). Ten copies of the dataset were created with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of participants. Each dataset was then analyzed and the results from each dataset were pooled into a final result using Rubin's rule [16]. Lastly, a sensitivity analysis using a Cox model stratified on the center variable was also performed. Hazard ratios and their 95% confidence interval were estimated. A *p* value < 0.05 was considered statistically significant. Statistical analyses were conducted with R v3.5.1.

Results

Participating ICUs and Patients Enrolled

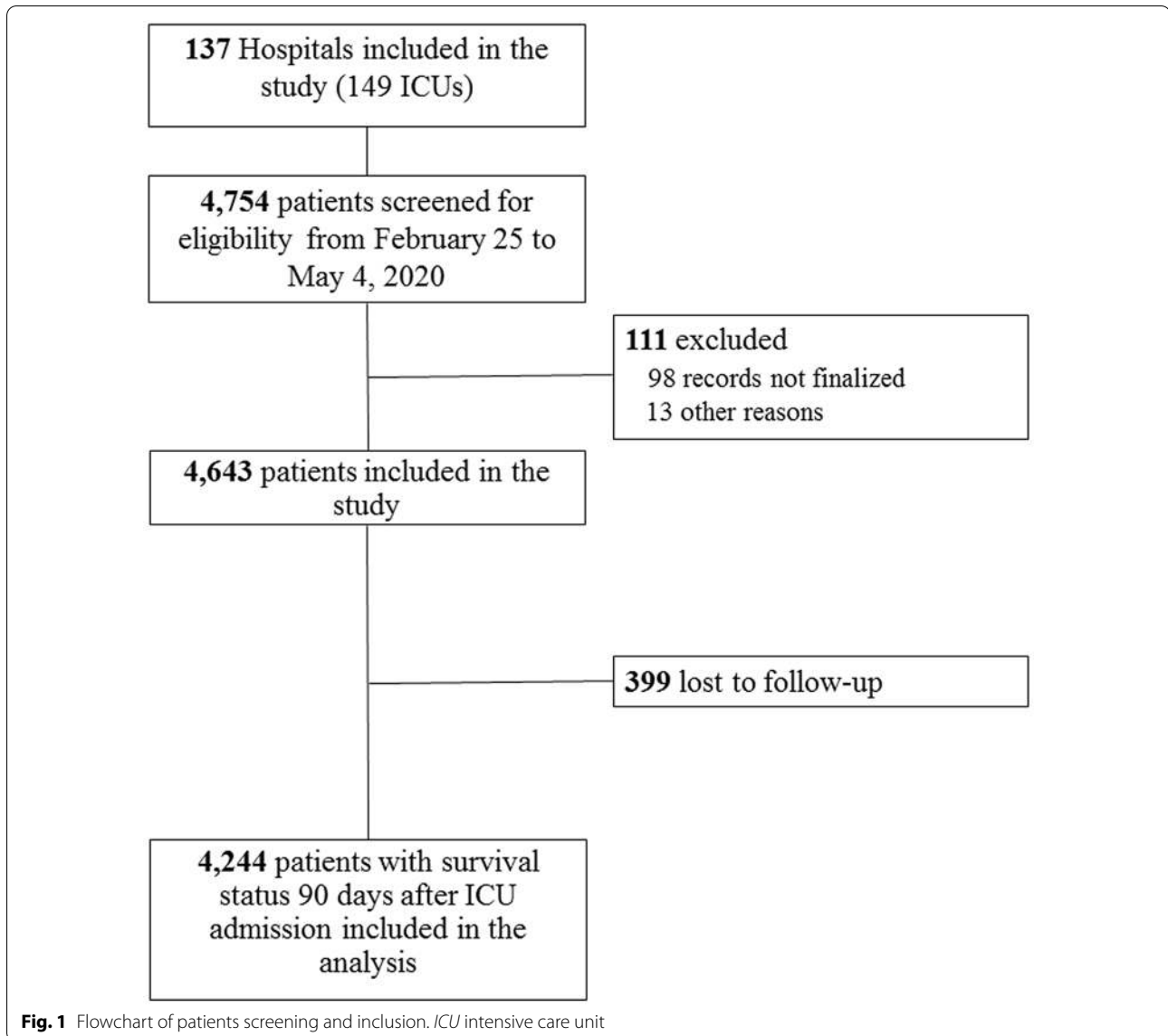
Patients were included in 149 ICUs (71 [48%] university, 66 [44%] public regional, and 12 [8%] private, semi-private, or military hospitals, respectively) from 138 centers in three countries. The median (interquartile) number of ICU beds in these centers and these ICUs were 26 (18–55) and 20 (14–28), respectively. Fifty-six percent of the patients were recruited in Paris and the surrounding area (see Table S1–S3 in the Supplement for an extensive description of ICUs and center characteristics). Ninety-four percent of the centers reported having extended the number of ICU beds during the COVID-19 outbreak.

Of the 4643 patients enrolled on May 4, 2020, 399 were lost to follow-up at Day-90. Thereafter we describe the characteristics of the remaining 4244 patients with available day-90 vital status (Fig. 1).

There were 1085/4244 (26%) female patients (Table 1). At ICU admission, their median (interquartile) age, SAPS II, and SOFA scores were 63 (54–71) years, 37 (28–50), and 5 (3–8), respectively. The rate of obese (BMI ≥ 30 kg/m²) patients was 1607/3935 (41%). The most frequent comorbidities were hypertension 2018/4197 (48%), known diabetes 1167/4196 (28%), and immunocompromised status 314/4192 (7%). Median (IQR) time between first symptoms and ICU admission was 9 (6–12) days. Of note, only 176/4124 (4%) patients were active smokers and only 208/4116 (5%) had concomitant bacterial pneumonia at ICU admission.

Ventilatory support, adjunctive therapies, and ARDS severity

On day-1, standard oxygen therapy, high flow oxygen, and non-invasive ventilation were applied to 1219/4157 (29%), 786/4096 (19%), and 230/4109 (6%) patients, respectively. The use of these modalities tended to increase over time (Table S5 and Figure S3). 2635/4175 (63%) were placed on invasive mechanical ventilation during the first 24 h, whereas in total 3376/4209 (80%) were intubated during their ICU stay. On the first day



in ICU, median tidal volume, PEEP, plateau, driving pressures, and mechanical power were 6.1 (5.8–6.7) mL/kg, 12 (10–14) cmH₂O, 24 (21–27) cmH₂O, 13 (10–17) cmH₂O, and 26.5 (18.6–34.9) J/min, respectively (Table 1). 1841/2560 (72%) patients required a FiO₂ ≥ 50%, while 1371 (54%) received a PEEP ≥ 12 cmH₂O.

Mild, moderate, and severe ARDS was reported in 539/2233 (24%), 1154/2233 (52%), and 540/2233 (24%) patients on mechanical ventilation (invasive or non-invasive) on ICU day 1, respectively (Table 2). Continuous neuromuscular blockade and prone position were used in 1966/2224 (88%), and 1556/2223 (70%) in these patients. Moderate and severe ARDS patients were more likely to receive these adjunct therapies,

with a median number of 3 (IQR 2–6) prone positioning sessions per patient. Of note, 888/2224 (41%) of them received corticosteroids for a median of 5 (IQR 2–8) days. Lastly, 321/4187 (8%) patients were placed on extracorporeal membrane oxygenation (ECMO). Table S6 provides the use of adjunct therapies in the whole cohort of 4224 patients.

ICU complications and organ support in patients intubated on ICU-day 1

Ventilator-associated pneumonia was diagnosed in 1209/2101 (58%) patients who were intubated on ICU day 1, whereas 623/2227 (28%) patients had an acute kidney failure requiring renal replacement therapy

Table 1 Demographic, clinical, and ventilatory support characteristics of 4244 patients according to their 90-day survival status

	No.	All patients (n = 4244)	90-day status		P value
			Alive (n = 2946)	Death (n = 1298)	
Age, years,	4244	63 (54–71)	61 (52–69)	68 (59–74)	< 0.001
Women, no (%)	4226	1085 (26)	771 (26)	314 (24)	0.170
Body mass index, kg/m ²	3935	28 (25–32)	29 (26–32)	28 (25–32)	0.006
≥ 30 kg/m ²		1607 (41)	1167 (42)	440 (37)	0.004
Active smokers	4124	176 (4)	116 (4)	60 (5)	0.234
SAPS II score	3935	37 (28–50)	34 (27–46)	44 (33–58)	< 0.001
SOFA score at ICU admission	3676	5 (3–8)	4 (3–8)	7 (4–10)	< 0.001
Treated hypertension	4197	2018 (48)	1310 (45)	708 (55)	< 0.001
Known diabetes	4196	1167 (28)	704 (24)	463 (36)	< 0.001
Immunodeficiency ^a	4192	314 (7)	178 (6)	136 (11)	< 0.001
Long-term corticosteroids ^b	4178	178 (4)	94 (3)	84 (7)	< 0.001
Clinical frailty scale	3152	2 (2–3)	2 (2–3)	3 (2–4)	< 0.001
Time between					
First symptoms to ICU admission, days	4007	9 (6–12)	9 (7–12)	8 (5–11)	< 0.001
ICU admission to invasive MV, hours	2010 ^c	8 (1–27)	9 (1–27)	7 (1–29)	0.482
During the first 24 h in ICU^b					
Standard oxygen therapy	4157	1219 (29)	927 (32)	292 (23)	< 0.001
High-flow oxygen	4096	786 (19)	584 (21)	202 (16)	< 0.001
Noninvasive ventilation	4109	230 (6)	134 (5)	96 (8)	< 0.001
Invasive mechanical ventilation	4175	2635 (63)	1678 (58)	957 (75)	< 0.001
PaO ₂ /FiO ₂	2500	154 (106–223)	163 (116–229)	136 (91–206)	< 0.001
VT, mL/kg PBW	2306	6.1 (5.8–6.7)	6.1 (5.8–6.6)	6.1 (5.7–6.7)	0.652
Set PEEP, cm H ₂ O	2542	12 (10–14)	12 (10–14)	12 (10–14)	0.429
Plateau pressure, cmH ₂ O	1847	24 (21–27)	24 (21–26)	25 (21–28)	< 0.001
Driving pressure, cmH ₂ O ^d	2256	13 (10–17)	12 (10–16)	14 (11–18)	< 0.001
Static compliance, mL/cmH ₂ O ^e	1746	33 (26–42)	34 (27–43)	32 (24–41)	< 0.001
< 30		635 (36)	367 (33)	268 (43)	< 0.001
30–39		562 (32)	380 (34)	182 (29)	
≥ 40		549 (31)	376 (33)	173 (28)	
Dynamic compliance, mL/cmH ₂ O ^f	409	17 (14–25)	18 (14–26)	17 (13–22)	0.010
Mechanical power, J/min ^g	1987	26.5 (18.6–34.9)	26.1 (18.4–34.2)	27.1 (18.9–36.1)	0.120
Ventilatory ratio ^h	2251	1.7 (1.4–2.2)	1.7 (1.4–2.1)	1.8 (1.4–2.3)	0.017
Concomitant bacterial pneumonia	4116	208 (5)	138 (5)	70 (6)	0.298
Hemodynamic component of the SOFA,	4065	1 (0–4)	0 (0–3)	3 (0–4)	< 0.001
Renal component of the SOFA,	4014	0 (0–1)	0 (0–0)	0 (0–1)	< 0.001
Corticosteroids ⁱ	4134	459 (11)	278 (10)	181 (14)	< 0.001
Blood gases					
pH	4003	7.41 (7.34–7.46)	7.43 (7.36–7.47)	7.38 (7.30–7.44)	< 0.001
PaCO ₂ , mmHg	4004	40 (35–46)	39 (35–45)	41 (35–49)	< 0.001
PaO ₂ /FiO ₂ ^j	3080	154 (103–222)	162 (112–227)	134 (90–205)	< 0.001
HCO ₃ , mmol/L	3942	25 (22–27)	25 (23–27)	24 (21–27)	< 0.001
Lactate, mmol/L	3795	1.2 (0.9–1.6)	1.2 (0.9–1.5)	1.3 (1.0–1.8)	< 0.001
Biology					
Lymphocyte count, × 10 ⁹ /L	3481	0.8 (0.6–1.2)	0.8 (0.6–1.2)	0.8 (0.5–1.1)	< 0.001
Platelet count, × 10 ⁹ /L	3867	224 (167–291)	230 (176–299)	205 (151–271)	< 0.001
Total bilirubin, μmol/L	3029	10 (7–14)	10 (7–14)	10 (7–16)	0.210
Serum creatinine, μmol/L	3915	78 (61–112)	73 (59–98)	94 (69–152)	< 0.001

Table 1 (continued)

	No.	All patients (n = 4244)	90-day status		P value
			Alive (n = 2946)	Death (n = 1298)	
D-dimers, µg/L	1697	1600 (897–3690)	1450 (843–3212)	2200 (1127–5516)	< 0.001

Results are expressed as n (%) or median (25th–75th percentiles)

FiO₂ fraction of inspired oxygen, *HCO₃* bicarbonate, *PEEP* positive end-expiratory pressure, *PaCO₂* partial pressure of carbon dioxide, *PBW* predicted body weight, *PaO₂* partial pressure of oxygen, *SAPS* simplified acute physiology score, *SOFA* Sequential Organ Failure Assessment, *VT* tidal volume

^a Defined as hematological malignancies, active solid tumor, or having received specific anti-tumor treatment within a year, solid-organ transplant, human immunodeficiency virus, or immunosuppressants

^b Several ventilation modalities could have been used during the first 24 h

^c Time of intubation was available for 2010/3376 patients with invasive mechanical ventilation during their ICU stay

^d Defined as plateau pressure—PEEP; If plateau pressure was missing, peak pressure was considered instead

^e Defined as tidal volume/(Plateau pressure – PEEP)

^f Defined as tidal volume/(Peak pressure – PEEP)

^g Mechanical power (J/min) = 0.098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure

^h Defined as (minute ventilation × PaCO₂) – (predicted bodyweight × 100 × 37.5)

ⁱ Irrespective of the dose and the indication

^j Calculated for all patients, including those on oxygen therapy using conversion tables provided in the online supplement

(Table 2). A venous thromboembolic complication was diagnosed in 373/2226 (17%) patients, of whom 207/2226 (9%) had proven pulmonary embolism.

Patient outcomes and predictors of 90-day mortality

Overall 90-day mortality was 31%. Within the first 7 days after ICU admission, 64 (12%, 95 confidence interval [CI], 9–15%) patients with mild and 183 (16%, 95 CI 14–18%) with moderate ARDS progressed to severe ARDS. In patients on mechanical ventilation (invasive or non-invasive) at ICU day one, 90-day mortality was 820/2233 (37%), and increased with the severity of ARDS at ICU admission (30%, 34% and 50% in mild, moderate, and severe ARDS patients, respectively) (Table 3 and Fig. 2). 90-day mortality was 292/1219 (24%), 202/786 (26%), and 96/230 (42%) in patients who received standard oxygen therapy, high flow oxygen, or non-invasive ventilation at day-1. Noticeably, 90-day mortality declined over time from 42 to 25% ($p < 0.001$) in the first and the last period, respectively (Table S5 and Figure S3). Of note, 90-day mortality was 36% in patients intubated during their ICU stay and 11% for those not intubated (see Table S7). The overall median durations of mechanical ventilation, ICU, and hospital stay for 90-day survivors were 13 (8–18), 21 (13–36), and 30 (20–48) days, respectively. Of note, these durations increased with the severity of the ARDS (Table 3).

Results of the multivariable analysis are reported in Table 4. After inspection of the proportional hazard assumption, a time-varying effect was introduced in the multivariate Cox model for four variables: body mass

index, active smoking, renal component of the SOFA score, and lymphopenia. Thus, for these variables, two types of hazard ratio are reported, indicating the early effect (before 14 days of follow-up) or the late effect (after 15 days of follow-up) of the corresponding baseline characteristic on the risk of death, respectively.

Non-survivors were older, and more frequently diabetic or immunocompromised than survivors. At ICU admission, they had a higher renal and hemodynamic SOFA component scores and lower PaO₂/FiO₂ ratio. Interestingly, they also had a shorter time since the onset of the first symptoms. Day-1 patients' characteristics significantly associated with higher 90-day mortality identified by the Cox regression model were older age, known diabetes, class 2 and extreme obesity, immunodeficiency, higher renal and cardiovascular components of the SOFA score, lower PaO₂/FiO₂, lower pH, and a shorter time between first symptoms and ICU admission (Table 4). The same analysis re-run after multiple imputations of missing data (Table S8), and a sensitivity analysis introducing the center variable as a stratification variable in the multivariable model yielded similar results (Table S9). Kaplan–Meier survival estimates according to age, ICU admission period, the renal component of the SOFA score, the delay between the first symptoms and ICU admission, immunocompromised status, diabetes, severe lymphopenia, and static pulmonary compliance categories at day-1 are provided in Figs. 2b, S4–S10. Lastly, outcomes of patients who progressed from mild to moderate or severe ARDS and those who progressed from moderate to severe ARDS within the first week of mechanical ventilation are reported in Fig. 2c, d.

Table 2 Use of adjunct measures, organ dysfunction and major complications according to acute respiratory distress syndrome severity for patients on mechanical ventilation (invasive or non-invasive) on ICU day 1

Parameter	No.	All ^a (n = 2233)	Mild ARDS ^b (n = 539)	Moderate ARDS ^c (n = 1154)	Severe ARDS ^d (n = 540)	P value
Ventilatory features on Day-1						
Plateau pressure, cmH ₂ O	1617	24 (21–27)	24 (21–26)	24 (21–27)	25 (22–28)	<0.001
Driving pressure, cmH ₂ O ^e	1965	13 (10–17)	12 (10–15)	13 (10–18)	14 (11–18)	<0.001
Static compliance, mL/cmH ₂ O ^f	1531	33 (26–42)	36 (29–44)	33 (26–42)	30 (24–37)	<0.001
Mechanical power, J/min ^g	1735	26.6 (18.7–34.9)	24.9 (18.3–33.3)	26.4 (18.5–34.4)	29.1 (20.3–37.6)	0.001
Tracheotomy	2229	198 (9)	53 (10)	107 (9)	38 (7)	0.207
Prone position	2223	1556 (70)	308 (57)	822 (71)	426 (79)	<0.001
Number of session	1553	3 (2–6)	3 (2–6)	3 (2–6)	3 (2–6)	0.585
Continuous neuromuscular blockers	2224	1966 (88)	441 (82)	1025 (89)	500 (93)	<0.001
Nitric oxide	2224	425 (19)	74 (14)	206 (18)	145 (27)	<0.001
Corticosteroids ^h	2224	888 (41)	192 (37)	458 (41)	238 (46)	0.012
ECMO	2153	235 (11)	41 (8)	111 (10)	83 (15)	<0.001
Cardiac arrest	2227	133 (6)	31 (6)	58 (5)	44 (8)	0.038
Thromboembolic complications	2226	373 (17)	107 (20)	174 (15)	92 (17)	0.043
Pulmonary embolism		207 (9)	59 (11)	95 (8)	53 (10)	0.872
Proven distal venous thrombosis		184 (8)	54 (10)	89 (8)	41 (8)	0.567
Renal replacement therapy	2227	623 (28)	135 (25)	320 (28)	168 (31)	0.080
Bacterial coinfection	1951	144 (7)	24 (5)	84 (8)	36 (8)	0.062
Ventilator-associated pneumonia	2101	1209 (58)	276 (54)	628 (58)	307 (61)	0.084

Definition of abbreviations: ECMO extracorporeal membrane oxygenation. Results are expressed as n (%) or median (25th–75th percentiles)

^a Only patients on invasive mechanical ventilation or non-invasive ventilation within the first 24 h in ICU

^b Defined as $200 \text{ mmHg} < \text{PaO}_2/\text{FIO}_2 \leq 300 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$ or continuous positive airway pressure $\geq 5 \text{ cm H}_2\text{O}$

^c Defined as $100 \text{ mmHg} < \text{PaO}_2/\text{FIO}_2 \leq 200 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$

^d Defined as $\text{PaO}_2/\text{FIO}_2 \leq 100 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$

^e Defined as plateau pressure – PEEP; If plateau pressure was missing, peak pressure was considered instead

^f Defined as tidal volume/(plateau pressure – PEEP)

^g Mechanical power (J/min) = $0.098 \times \text{tidal volume} \times \text{respiratory rate} \times (\text{peak pressure} - 1/2 \times \text{driving pressure})$. If not specified, peak pressure was considered equal to plateau pressure

^h Irrespective of the indication, the dose, and the timing

Discussion

We report herein one of the largest prospective case-series of COVID-19 patients who required intensive care admission, with detailed information on their baseline characteristics, ARDS severity, and 90-day outcomes. Overall 90-day mortality was 31% and was higher in older and obese patients, diabetics, immunocompromised patients, and those who had multiple organ dysfunction at ICU admission. 90-day mortality rates were 30%, 34%, and 50%, in patients with mild, moderate, and severe ARDS who were on mechanical ventilation (invasive or non-invasive) on ICU day-1, respectively. Noticeably, mortality rates decreased over time during the study period, while ICU and hospital length of stay were substantially longer than in other cohorts of ARDS patients [17].

Acute respiratory failure was the main indication for ICU admission, with 80% of our COVID-19 patients

requiring invasive mechanical ventilation which is consistent with the experience in Lombardy, Italy [2], where 88% of ICU patients were intubated. However, lower rates of intubation in ICU patients were reported in Wuhan, China by Wang et al. (47%), and Yang et al. (42%) [18, 19], and in Washington state, USA (71%) [20]. While early single-center reports in small groups of COVID patients reported well-preserved lung mechanics despite the severity of hypoxemia [21], more recent data [22] and our observations suggested that lung compliance and driving pressure were close to those of reported in classical ARDS. Mechanical power which is the energy delivered to the respiratory system over time during mechanical ventilation was very high in our patients with ARDS, reaching 26.5 (18.6–34.9) J/min, while a higher mortality risk has been suggested for patients with ARDS whose value exceeded 17 J/min [23]. In that context, the application of evidence-based

Table 3 Outcome of patients on mechanical ventilation (invasive or non-invasive) according to Acute Respiratory Distress Syndrome Severity assessed the first day in the ICU

Parameter	No.	All ^a (n = 2233)	Mild ARDS ^b (n = 539)	Moderate ARDS ^c (n = 1154)	Severe ARDS ^d (n = 540)	P value ^e
Progression of ARDS severity, No (%) [95 CI]	2233	2233	539 (24) [22–26]	1154 (52) [50–54]	540 (24) [22–26]	
Progression to moderate ^c			237 (44) [40–48]	–	–	
Progression to severe ^d			64 (12) [9–15]	183 (16) [14–18]	–	
Duration of invasive ventilation, days	1448					
All patients		12 (7–17)	11 (6–17)	12 (7–17)	11 (6–17)	0.021
Surviving patients at day-90		13 (8–18)	12 (6–18)	14 (8–18)	14 (10–19)	0.007
ICU length of stay, days	2187					
All patients		16 (9–28)	15 (8–27)	17 (9–28)	16 (8–30)	0.149
Surviving patients at day-90		21 (13–36)	18 (10–31)	21 (13–35)	26 (16–43)	< 0.001
ICU mortality	2214	773 (35)	146 (27)	366 (32)	261 (49)	< 0.001
Hospital length of stay, days	2041					
All patients		23 (12–39)	22 (13–39)	24 (13–40)	22 (9–36)	0.002
Surviving patients at day-90		30 (20–48)	28 (17–47)	31 (20–47)	32 (23–49)	0.012
Hospital mortality	2086	797 (38)	154 (30)	375 (35)	268 (53)	< 0.001
Still in the hospital at day-28		1152 (53)	286 (54)	628 (56)	238 (45)	< 0.001
Day-28 mortality	2233	703 (31)	134 (25)	331 (29)	238 (44)	< 0.001
Day-60 mortality	2233	808 (36)	157 (29)	382 (33)	269 (50)	< 0.001
Day-90 mortality	2233	820 (37)	162 (30)	388 (34)	270 (50)	< 0.001

Results are expressed as n (%) or median (25th–75th percentiles)

ARDS acute respiratory distress syndrome, ICU intensive care unit

^a Only patients on invasive mechanical ventilation or non-invasive ventilation within the first 24 h in the ICU

^b Defined as $200 \text{ mmHg} < \text{PaO}_2/\text{FIO}_2 \leq 300 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$ or continuous positive airway pressure $\geq 5 \text{ cm H}_2\text{O}$

^c Defined as $100 \text{ mmHg} < \text{PaO}_2/\text{FIO}_2 \leq 200 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$

^d Defined as $\text{PaO}_2/\text{FIO}_2 \leq 100 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$

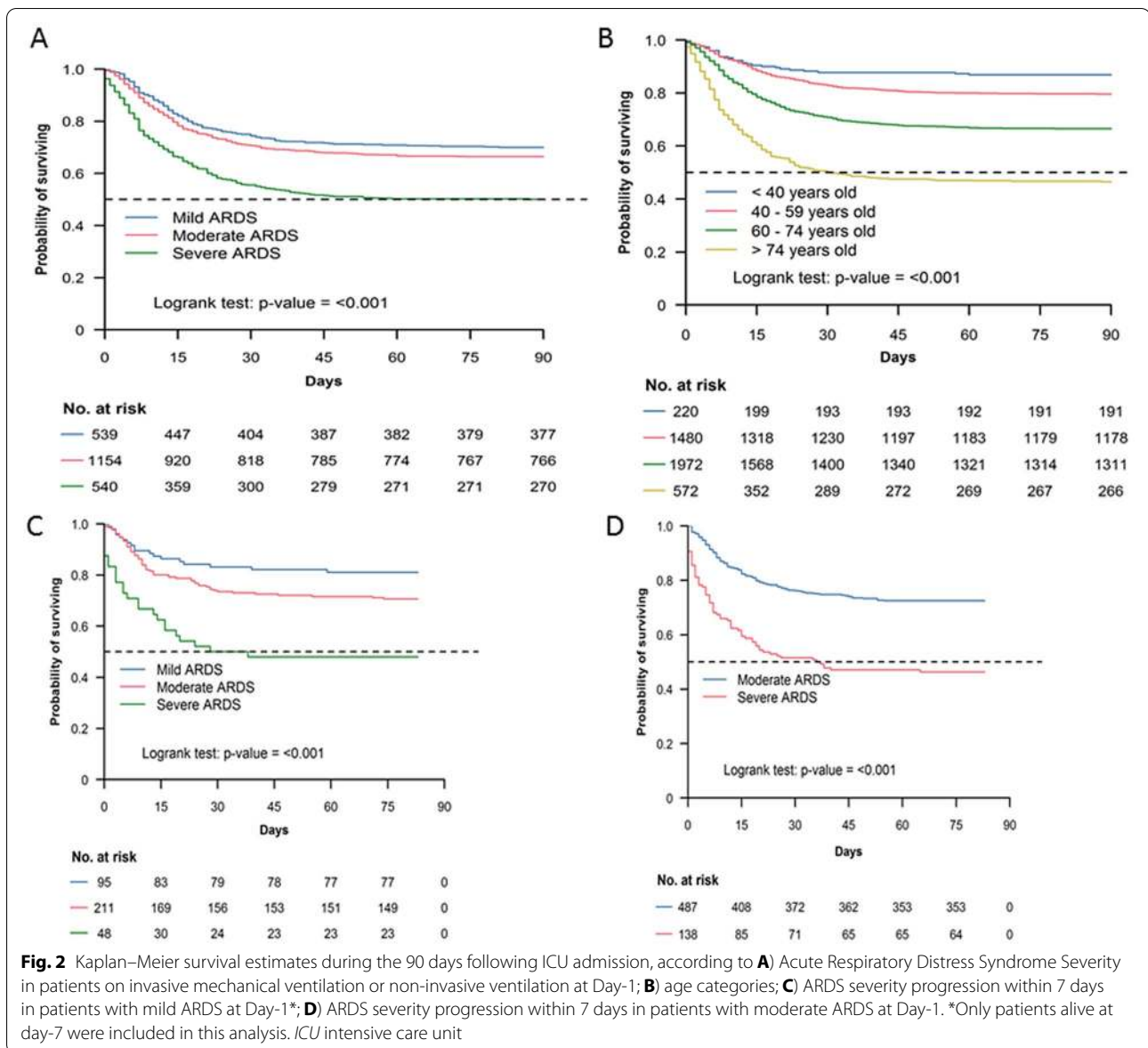
^e p global value

ARDS care, such as lung-protective mechanical ventilation and proning are both warranted [24]. ECMO, which was used in 15% of severe ARDS in our cohort should be considered when these measures have failed [25].

28-day mortality was 39% in 257 critically-ill COVID-19 patients in New-York city, of whom 203 (79%) received invasive mechanical ventilation [4], 41% in patients on invasive mechanical ventilation included in the usual care group of the RECOVERY randomized trial [6] and >50% in 733 Chinese patients admitted in the ICU [3]. Despite similar severity at baseline, day-28 mortality were 26% in the whole cohort and 30% in our patients intubated at day-1, a rate close to that reported in the large LUNG-SAFE study [17]. Different characteristics of patients admitted to ICUs and different degrees of stress on healthcare systems could explain these discrepancies [26]. Besides, we report a progressive decrease in 90-day

mortality over the study period with a higher proportion of patients on high flow oxygen and non-invasive ventilation and a lower rate of intubation on ICU day-1 in the last period of the study (Table S5 and Figure S3). Similar findings have been reported by other groups [27] and might reflect better knowledge of the pathophysiology of the disease over time and less reluctance to use non-invasive oxygenation strategies. It should however be noticed that duration of invasive mechanical ventilation and length of ICU and hospital stays were substantially longer than those of in ARDS unrelated to COVID-19. For instance, ICU length of stay in patients surviving severe ARDS was 26 (13–43) days, compared to 14 (7–23) days in the LUNG-SAFE study [17]. These patients rapidly overwhelmed ICU's capacity, forcing a major reorganization of ICU beds during the crisis [28].

Identifying the determinants of outcomes of critically ill patients with severe COVID-19 is crucial to optimize



the use of ICU care and other hospital resources. Older age, obesity, diabetes, being immunocompromised, lower $\text{PaO}_2/\text{FiO}_2$ and higher hemodynamic and renal SOFA score at ICU admission were independently associated with 90-day mortality, highlighting the dismal impact of premorbid conditions and multiorgan damage on the outcomes of patients with the most severe forms of COVID-19 [3, 29]. The rate of patients with a $\text{BMI} \geq 30 \text{ kg/m}^2$ was 41% in our cohort and unusually high compared to the prevalence of obesity in the French population [30]. More severe COVID-19 in obese patients may be explained by impairments in the adaptive immune response [31], cardiometabolic and thrombotic derangements [32], and alterations in lung function [33].

Obesity may also be a marker of poorer baseline health conditions since it is frequently associated with a lower socio-economic status [34]. As previously reported [35], a shorter time between first symptoms and ICU admission was also independently associated with increased mortality. Lastly, we and others [36, 37] observed an unusually high rate of thromboembolic complications, with 9% of proven pulmonary embolism. This rate may likely be higher since pulmonary CT angiography was not systematically performed in all patients. Diffuse vascular endothelium injury and intense activation of the coagulation cascade may explain this increased risk of venous thrombosis [38].

Table 4 Predictive patient factors associated with 90-day mortality in critically ill adults with COVID-19

	No.	Univariate HR (95% CI)	P value	Multivariate HR (95% CI) ^a	P value
Age, years	4244	1.05 (1.04–1.05)	< 0.001	1.05 (1.04–1.06)	< 0.001
Date of ICU admission	4244		< 0.001		0.311
Before March, 15		–		–	
From March, 16 to 31		0.69 (0.56–0.84)		0.86 (0.64–1.16)	
From April, 1 to 15		0.61 (0.50–0.76)		0.75 (0.54–1.04)	
After April, 16		0.54 (0.40–0.72)		0.82 (0.52–1.29)	
Immunodeficiency	4192	1.64 (1.38–1.96)	< 0.001	1.38 (1.06–1.80)	0.020
Body mass index, kg/m ^{2b}	3935		0.013		0.007
< 25		–		–	
25 ≤ BMI < 30		0.92 (0.68–1.25)		1.06 (0.78–1.43)	
30 ≤ BMI < 35		0.77 (0.57–1.03)		0.81 (0.60–1.10)	
35 ≤ BMI < 40		0.94 (0.68–1.29)		1.11 (0.80–1.55)	
≥ 40		0.59 (0.42–0.83)		0.63 (0.44–0.89)	
≥ 40		1.16 (0.79–1.69)		1.50 (1.02–2.21)	
≥ 40		0.49 (0.30–0.79)		0.60 (0.37–0.97)	
≥ 40		1.47 (0.93–2.33)		2.05 (1.28–3.27)	
≥ 40		0.60 (0.32–1.14)		0.87 (0.45–1.66)	
Active smoking ^b	3935	1.51 (0.96–2.36)	0.225	1.30 (0.82–2.05)	0.314
Active smoking ^b		0.87 (0.45–1.70)		0.71 (0.36–1.39)	
Treated hypertension	4197	1.44 (1.29–1.60)	< 0.001	1.01 (0.85–1.19)	0.940
Known diabetes	4196	1.62 (1.44–1.81)	< 0.001	1.51 (1.28–1.78)	< 0.001
Time between first symptoms to ICU admission, days	3862		< 0.001		0.010
< 4 days		–		–	
4–7 days		0.87 (0.65–1.16)		1.07 (0.80–1.43)	
≥ 8 days		0.52 (0.39–0.70)		0.73 (0.54–0.98)	
During the first 24 h in the ICU					
CV component of the SOFA score ≥ 3	4065	1.77 (1.58–1.98)	< 0.001	1.79 (1.52–2.11)	< 0.001
Renal component of the SOFA score ≥ 3 ^b	4014	3.01 (2.30–3.92)	< 0.001	2.38 (1.81–3.13)	< 0.001
Renal component of the SOFA score ≥ 3 ^b		1.66 (1.11–2.48)		1.32 (0.87–2.01)	
Coagulation component of the SOFA score ≥ 3	4002	2.01 (1.21–3.34)	0.016	1.73 (0.81–3.69)	0.190
PaO ₂ /FiO ₂ ^c	3080		< 0.001		< 0.001
200 < PaO ₂ /FiO ₂ ≤ 300		0.94 (0.72–1.21)		0.93 (0.67–1.29)	
100 < PaO ₂ /FiO ₂ ≤ 200		1.09 (0.87–1.38)		1.12 (0.83–1.51)	
PaO ₂ /FiO ₂ ≤ 100		1.73 (1.36–2.19)		2.05 (1.51–2.78)	
Lymphocyte count ≤ 1 × 10 ⁹ /L ^b	3481	0.92 (0.75–1.14)	0.008	0.80 (0.65–0.99)	0.030
Lymphocyte count ≤ 1 × 10 ⁹ /L ^b		1.46 (1.14–1.88)		1.24 (0.96–1.60)	
pH	4003	0.67 (0.60–0.75)	< 0.001	0.80 (0.65–0.97)	0.065

BMI body mass index, CV cardiovascular, SOFA Sequential Organ Failure Assessment, ICU intensive care unit, HR hazard ratio, CI confidence interval

^a Complete analysis cases on 2152 patients

^b Early effect before 14 days of follow-up (first line); late effects (i.e., after day-15) in the second line

^c Calculated for all patients, including those on oxygen therapy using conversion tables provided in the online supplement

The major strength of this study is the detailed report of physiological, clinical features, ventilatory management, and 90-day outcomes of a large, multicenter series of 4244 critically ill COVID-19 patients. We acknowledge several limitations to our study. First, we conducted this cohort at a time where the national health system was extremely pressured with a need for a large number of

ICU beds in some regions. Then, we cannot rule out that ICU admission policies and patients' management were similar in all centers, although a sensitivity analysis introducing the center variable in the multivariable model found similar results. Second, testing was not standardized across sites, which might have led to misclassification. Third, some variables have missing data (as reported

in the tables) due to a large number of patients included in a short period and intense clinical activity during the crisis. Indeed, our multivariable model included only 51% of the whole cohort of patients because of these missing data, which may explain, together with other residual confounders, the unanticipated lower mortality before 14 days of follow-up associated with baseline lymphopenia [39, 40]. However, this association was no longer statistically significant in the model with multiple imputations. Fourth, Grasselli et al. recently reported that high D-dimer concentration was significantly associated with mortality in COVID-19-related ARDS patients when associated with low values of static respiratory system compliance [22]. Unfortunately, we were unable to confirm that result in our multivariable model due to inconsistent collection of this data at ICU admission.

Conclusions

In this case series of 4244 critically ill patients with laboratory-confirmed COVID-19 admitted to our ICUs, overall 90-day mortality was 31% and decreased over time during the study period. Mortality was higher in older patients, immunocompromised, extreme obese, diabetics, those with a shorter delay between first symptoms and ICU admission, and those with extra-pulmonary organ dysfunction at ICU admission. Ninety-day mortality increased with the severity of ARDS from 30% in mild to 50% in severe ARDS. These information, together with the very long durations of mechanical ventilation and of ICU stay, which have contributed to the swamping of our ICU's capacity, will be critical for the management of the second wave of the epidemic. Lastly, long-term follow-up is warranted to provide a complete description of the outcomes and potential sequelae associated with the most severe forms of COVID-19 requiring ICU treatment.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-020-06294-x>) contains supplementary material, which is available to authorized users.

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Author contributions

MS and DH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: GB, AC, AD, MD, DH, AK, AM, TP, MS. Methodology: DH. Acquisition, analysis, or interpretation of data: AC, AD, MD, DH, AK, AM, TP, MS. Drafting of the manuscript: AC, AD, DH, MS. Critical revision of the manuscript for important intellectual content: GB, MD, AK, AM, TP. Statistical analysis: DH, SL. Supervision: AC, AD, AM. Obtained funding: AD, DH, JP, MS. Administrative, technical, or material support: JP, FP.

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Compliance with ethical standards

Conflicts of interest

MS reported personal fees from Getinge, Dräger, and Xenios, outside the submitted work. AD reports personal fees from Medtronic, grants, personal fees and non-financial support from Philips, personal fees from Baxter, personal fees from Hamilton, personal fees and non-financial support from Fisher & Paykel, grants from French Ministry of Health, personal fees from Getinge, grants and personal fees from Respinor, grants and non-financial support from Lungpacer, outside the submitted work. AM reported personal fees from Faron Pharmaceuticals, Air Liquid Medical Systems, Pfizer, Resmed and Draeger and grants and personal fees from Fisher and Paykel and Covidien, outside this work. MD reported personal fees from Lungpacer. AK reported personal fees from Aspen, Aguetant and MSD. No other disclosures were reported.

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