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Invasive mechanical ventilation during the first wave of COVID-19: Management and outcomes

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Abstract

***Objective*: To describe demographics, clinical, and respiratory mechanics (including ventilatory management details) of patients admitted to the Intensive Care Unit (ICU) with severe COVID-19 and to evaluate the effectiveness of gas exchange variables, ventilatory parameters, and ICU illness severity scores in predicting 28-day mortality.**

***Design*: Single-center retrospective cohort study.**

***Setting*: Portuguese medical-surgical ICU.**

***Patients*: Adults sequentially admitted to the ICU, from March 18 to May 12, 2020, with critical COVID-19 requiring invasive mechanical ventilation (IMV) for over 48 hours.**

***Interventions*: None, due to study design.**

***Measurements and results*: Data regarding positioning, positive end-expiratory pressure (PEEP), driving pressure, static lung compliance, and lowest daily arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) ratio throughout the first 5 days of ICU admission were collected from daily ventilatory assessment charts. The median ICU length of stay was 11.3 days and median IMV duration was 9.5 days. The 28-day mortality was 12.1%. When comparing non-survivors and survivors, significant differences were found regarding Simplified Acute Physiology Score (SAPS) II (48.5, IQR 14.0 vs. 32.0, IQR 11.0, p=0.004), PaO2/FiO2 ratio before endotracheal intubation (101.3, IQR 22.5 vs. 174.1, IQR 9.5, p=0.01) and throughout ICU stay. Over 90% of patients were submitted to prone positioning. Use of low PEEP levels and maintenance of low driving pressures in patients whose overall compliance was low as possible.**

***Conclusions*: Significant differences were found regarding SAPS II and PaO2/FiO2 ratios between survivors and non-survivors, eliciting further investigation as potential mortality predictors. With the second wave of the pandemic taking shape, sharing previous experience is crucial to further coordinate efforts internationally.**

Key words: COVID-19, lung compliance, prone position, severe acute respiratory syndrome coronavirus 2, Intensive Care Units, respiratory mechanics.

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Introduction

Given the rapid increase in the number of cases of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide, as of March 11, 2020, the World Health Organization determined this outbreak could be characterized as a pandemic. (1) In Portugal, the first case of coronavirus disease 2019 (COVID-19) was identified on March 2, 2020. On March 18, a national emergency state was declared and further extended up until May 2. Considering the incoming reports from colleagues stressing the burden upon intensive care

practice, preparedness became a priority in Centro Hospitalar de Entre o Douro e Vouga, a tertiary hospital in Santa Maria da Feira, Aveiro, Portugal. (2-4) Moreover, the hospital catchment area included the Ovar municipality, where a calamity state was issued due to first epidemiological evidence of active community transmission of SARS-CoV-2 in Portugal, implying the only local mandatory lockdown in mainland.

The Intensive Care Medicine Department promptly doubled its bed capacity, assigning COVID-19 patients to a physically independent cohort. A team of intensivists dedicated to critically ill COVID-19 patients was created, as well as a daily appointed intensivist in charge of evaluating COVID-19 patients from general wards flagged by clinicians as being in potential need of level of care escalation.

Patients admitted to the Intensive Care Unit (ICU) due to severe hypoxic respiratory failure requiring invasive mechanical ventilation posed a challenge in terms of management, particularly as to which strategy to pursue in order to optimize ventilation and, lastly, oxygenation.

This study described demographics, clinical, and ventilatory parameters of patients hospitalized with SARS-CoV-2 pneumonia requiring invasive mechanical ventilation in a Portuguese Medical-Surgical Hospital critical care unit. It also aimed to evaluate whether gas exchange variables, ventilatory parameters, and commonly used ICU illness severity scoring systems might be useful tools to predict 28-day mortality in this particular subset of patients.

Methods

This single-center retrospective cohort study included 18 years of age or older adults sequentially admitted to the ICU of a Portuguese Medical-Surgical Hospital with critical COVID-19 - defined by a positive polymerase chain reaction (PCR) test for SARS-CoV-2 infection via naso-oropharyngeal swab, with severe hypoxemia and/or the presence of other organ failure, including shock (5) - from March 18 to May 12, 2020. Only patients requiring over 48 hours of invasive mechanical ventilation were included. Although not included in the study population for sample homogeneity purposes, management of patients requiring high-flow nasal cannula (HFNC) and noninvasive positive pressure ventilation (NIPPV) modalities was performed in a level I unit (integrated in the Internal Medicine Department) and supervised by the Intensive Care Medicine Department. Inpatients with suspected COVID-19 on ICU admission with a subsequent negative SARS-CoV-2 reverse-transcriptase (RT)-PCR were excluded. Prior to data collection, an informed consent was obtained from the institutional review board.

Data regarding demographics, known comorbidities (based on Age-Adjusted Charlson Comorbidity Index), onset of symptoms, hospital and ICU admission, SAPS II, and Sequential Organ Failure Assessment (SOFA) scores (worst values during the first 24 hours of ICU admission) and the last arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) ratio before endotracheal intubation were collected. The time stamp for mechanical ventilation initiation was defined as date and hour of ICU admission. The lowest daily PaO2/FiO2 ratio (starting at the hour of ICU admission) was retrieved from the arterial blood samples collected every 4 hours throughout the first 5 days of ICU admission.

In light of the evidence available at the time of the surge of the first critically ill COVID-19 patients in Portugal, (6,7) ICU treatment protocol included, in addition to standard supportive care, hydroxychloroquine 400 mg twice a day on the first day, via nasogastric tube, followed by 200 mg twice a day from day 2 to day 10 of ICU admission. It also included azithromycin 500 mg intravenously daily for 5 days. Presence of QT prolongation or ventricular arrhythmias were encompassed on the protocol, as well as respiratory virus testing (influenza A, influenza B, and respiratory syncytial virus) upon ICU admission.

Antibiotics were initiated upon clinical and/or laboratory suspicion of bacterial superinfection (i.e., elevated leukocyte count with neutrophilia, de novo C-reactive protein elevation, procalcitonin level above 0.5 ng/ml, new onset of fever in a previously apyrexial patient), ultimately relying upon tailored clinical judgement. Whenever patients had persistent evidence of systemic inflammation suggestive of macrophage activation syndrome (i.e., elevated serum ferritin, D-dimer, and lactate dehydrogenase levels, as well as prominent hepatic dysfunction or thrombotic tendency), systemic glucocorticoid was initiated - methylprednisolone 1 mg per kilogram per day, tapered according to clinical response.

Focus relied upon ventilatory and gas exchange variables during the first 5 days of ICU stay. Lung-protective ventilation was the cornerstone of ventilatory management - low tidal volume (6 to 8 milliliters per kilogram of ideal body weight according to Devine's formula), targeting plateau pressures to less than 30 cmH2O, driving pressure less than 15 cmH2O, respiratory rate targeted for arterial pH above 7.25 and optimizing patient-ventilator synchrony with a neuromuscular block-

ing agent (rocuronium bromide), preferably in bolus and, if intravenous infusion required, for no longer than 48 hours straight. A PaO2/FiO2 ratio below 150 mmHg determined allocation to prone positioning. If a patient presented with a PaO2/FiO2 ratio below 100 mmHg or inability to ventilate within the safety thresholds, referral to an extracorporeal support center was considered.

A daily ventilatory assessment was performed by an intensivist for each patient, records from which data regarding positioning (dorsal decubitus or prone position), positive end-expiratory pressure (PEEP), driving pressure and static lung compliance were collected, as well as the number of sessions of prone positioning (sixteen hours per session).

The follow-up period was 28 days from ICU admission, consisting of revision of patients' electronical clinical processes.

Data were analysed using IBM® SPSS® Statistics 26.0 and interpreted by the authors.

Results

Out of a total of 311 hospital admissions due to COVID-19 from March 18 to May 12, 2020, 43 (13.8%) were admitted to the ICU due to disease severity. However, for the purpose of this study, 33 patients were included (differential explained by 2 patients with a length of stay under 12 hours, 5 patients who did not meet criteria for invasive mechanical ventilation, and 3 patients whose clinical status resolved with noninvasive mechanical ventilation alone), with a mean age of 61.7 years (standard deviation [SD] 2.1), the majority of which were male (69.7%). The median age-adjusted Charlson Comorbidity Index estimated 10-year survival was 77.5% (interquartile range [IQR] 36.8%), and the most common comorbidities were dyslipidemia (54.5%), arterial hypertension (42.4%), and uncomplicated diabetes mellitus (33.3%), with the majority of patients having at least one comorbidity (87.9%). The most commonly reported symptoms upon hospital admission were cough (87.9%), fever - defined by tympanic temperature over 38.2 ºC (72.7%), and dyspnea (51.5%). The majority of patients were admitted from general wards (60.6%) as their clinical condition deteriorated and a higher level of care was needed (**Table 1**).

The median time elapsed from symptom onset to hospital and ICU admission was 6 and 9 days (IQR 7), respectively. Once admitted to the hospital, patients requiring mechanical ventilation were admitted to the ICU within less than 48 hours (**Table 2**). The median SOFA score on the first 24 hours of ICU stay was 7 (IQR 2). The median ICU length of stay was 11.3 days (IQR 6.9), and patients required invasive mechanical ventilation for a median period of 9.5 days (IQR 8.1) (**Table 2**). Three patients (9.1%) underwent tracheostomy due to prolonged ventilatory weaning and one patient was referred to an extracorporeal membrane oxygenation center. Twenty-eight patients (84.4%) were treated with antibacterial agents and thirteen patients (39.4%) had systemic glucocorticoids therapy according to protocol, initiated within one week after ICU admission (median 6.8 days, IQR 8.1). One patient (3.0%) initiated renal replacement therapy due to oliguric acute kidney injury.

On day 28 after ICU admission, eighteen patients (54.5%) had been discharged from the hospital, seven (21.2%) were allocated to a post-acute care facility, three patients (9.1%) remained in the ICU, and one patient (3.0%) had been transferred to the Internal Medicine general ward due to level of care de-escalation. Twenty-eight-day mortality was 12.1% (n=4). No readmissions or losses occurred throughout the study follow-up period (**Table 3**).

Regarding presenting characteristics on ICU admission lymphopenia and a mean PaO2/FiO2 ratio of 165±9.7 mmHg were noteworthy, as well as the absence of relevant acid-base disorders or hyperlactacidemia. There was a significantly lower mean PaO2/FiO2 ratio before endotracheal intubation among non-survivors when compared to those who survived (101.3, IQR 22.5 vs 174.1, IQR 9.5, p=0.01). The mean SAPS II on ICU admission was 33.0 (IQR 17.0). A statistically significant difference was found between survivors and non-survivors' median SAPS II, the latter having the highest score (48.5, IQR 14.0 vs 32.0, IQR 11.0, p=0.004). Admission protocol involved respiratory virus testing, which was negative on the entire study population.

When analyzing ventilation strategy, the majority of patients (90.9%, n=30) were allocated to prone position according to protocol, with a median of 3 sixteen-hour sessions performed per patient. PaO2/FiO2 ratio on the first five days of ICU admission was consistently inferior in the non-survivors group, reaching statistical significance on days 1 and 3 (day 1: 140.9±6.0 vs 91.5±15.9 mmHg, p=0.008; day 3: 168.9±11.1 vs 107.8±5.7 mmHg, p<0.001) (**Table 4**).

The median values of tidal volume were located in 6.5-7.0 milliliters per kilogram of ideal body weight interval. Plateau pressure in all daily observations was below 30 cmH2O. With a median PEEP of 10 cmH2O, driving pressure median values during the first five days of invasive mechani-

cal ventilation varied between 11 and 13 cmH2O, with no relevant differences among survivors and non-survivors regarding these variables. Median static compliance ranged between 35 and 40.5 milliliters per cmH2O and, although not reaching statistical significance, there was a trend towards slightly higher compliance among non-survivors from days 2 to 5 of observation.

Discussion

Information regarding incidence, baseline characteristics, and outcomes in the critically ill COVID-19 patients is still lacking. Moreover, specifically when addressing mechanically ventilated patients data is scarcer.

A higher mortality risk on critically ill COVID-19 patients with preexisting cardiovascular disease or risk factors has been established. (8,9) Similar to previous works, (10) our results show nearly 88% of patients having at least one comorbidity, with dyslipidemia, arterial hypertension, and diabetes being the most common.

Grasseli G, et al (11) reported a 26% ICU mortality on a large case series with 88% of patients requiring mechanical ventilation. Mortality rates of COVID-19 patients under invasive mechanical ventilation range from 23.5% to 97%. (12-14) In this cohort, a 12.1% 28-day mortality rate was observed. Due to outreach networking, inpatients were referenced to the ICU within less than 48 hours of hospital admission, a potential concurrent factor to an inferior mortality rate. This time frame might also be worthy to take into account by clinicians in general wards, in order to flag those patients in a timely manner when the level of care escalation is necessary due to severe hypoxemic respiratory failure.

A mounting body of evidence finds the use of systemic glucocorticoids appropriate in mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS). (15) Although the criteria fulfillment and respiratory mechanics resemblance to those of typical ARDS remains controversial, (16) COVID-19 patients present with dysregulated inflammation and coagulation identical to that observed in ARDS. (17) Among the critically ill COVID-19 adults, it is not infrequent the combination of high levels of ferritin and D-dimer, hepatic dysfunction, and a thrombotic tendency, attributable to the occurrence of macrophage activation syndrome (MAS). (18) The recently published RECOVERY trial (19) of dexamethasone in hospitalized patients with COVID-19 proved 28 day-mortality benefits in mechanically ventilated patients. However, available evidence throughout this study inclusion period only suggested systemic glucocorticoids might reduce both mortality and duration of mechanical ventilation in the subset of patients with COVID-19 and ARDS. (20) Therefore, systemic glucocorticoids were initiated upon laboratory evidence of MAS, which occurred within the first week of ICU admission in this cohort.

Lymphopenia was a prominent laboratory finding, as previously reported in the critically ill COVID-19 patients. (21) Data collection was clinically driven and not systematic, a limitation hindering further characterization in terms of laboratory profile upon ICU admission, namely ferritin, D-dimer, lactate dehydrogenase, and troponin levels, suggested having a negative impact on mortality. (9,12)

SAPS II is a validated tool in European and Northern American ICU populations, (22) allowing score conversion to an in-hospital mortality probability. Since there were no patients with SARS-CoV-2 pneumonia in the original validation sample, it remains uncertain to which extent this tool is applicable in said context. In this cohort, non-survivors' SAPS II were significantly higher comparing to survivors, eliciting the possibility of being a reliable mortality predictor among the critically ill COVID-19 patients.

Hypoxemia is the most prominent gas exchange abnormality found on severe COVID-19 pneumonia. (23) The finding of a statistically significantly lower mean PaO2/FiO2 in spontaneous breathing among non-survivors is crucial to clinicians involved in the critically ill patient circuit. A lower PaO2/FiO2 in non-survivors was consistent throughout the first five days of ICU admission. Larger studies are needed to eventually establish PaO2/FiO2 cut-offs that, combined with clinical deterioration, might prompt immediate ICU referral, hence improving in-hospital care quality.

Recently, a classification of COVID-19 respiratory distress into two phenotypes, in a time-related disease spectrum, has been proposed: type L, characterized by nearly normal compliance and low lung recruit ability (i.e., poorer response to recruitment maneuvers and prone positioning), and type H, parallel to disease progression, with low compliance and higher lung recruit ability. (24) The subject of lung recruit ability was approached by Pan C, et al (25) with high driving pressure, low compliance, and poor lung recruit ability, improved by prone positioning, as the main findings. Following the principles of lung-protective ventilation, (15)

we managed to use low PEEP and maintain low driving pressure in patients whose overall compliance was low. The fact that it was possible to perform prone positioning in nearly 91% of patients might have contributed to the maintenance of safety thresholds in mechanical ventilation.

This study has its limitations, mainly due to study design, since data were acquired retrospectively and a small sample was analyzed. However, due to uncertainty regarding which strategy to pursue in order to optimize ventilation in the critically ill, requiring mechanical ventilation COVID-19 patients, we believe the evidence of this study may prove valuable not only to intensivists, but to each and every clinician managing this subset of patients worldwide. The findings of this study ought to be interpreted as exploratory, eliciting further investigation regarding the impact of invasive mechanical ventilation optimization strategies on clinical outcomes of the critically ill COVID-19 patients.

Conclusion

This study provides a description of demographics, clinical outcomes, and ventilatory management in critically ill patients with SARS-CoV-2 pneumonia requiring invasive mechanical ventilation. Statistically significant differences were found among survivors and non-survivors regarding SAPS II, arterial oxygen partial pressure to fractional inspired oxygen ratio before endotracheal intubation, and on days 1 and 3 of ICU admission. Further studies are needed to assess the robustness of the aforementioned variables as reliable mortality predictors. With the second wave of the pandemic taking shape, sharing previous experience is of the utmost importance in order to further coordinate efforts in a national and international rationale.

Acknowledgements

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Table 1. Baseline characteristics of mechanically ventilated patients with COVID-19

	n (%)
Demographics	
- Male sex	23 (69.7%)
- Age (years), mean (SD)	61.7 (2.1)
- Home municipality	
- Ovar	18 (54.5%)
- Santa Maria da Feira	5 (15.2%)
- Oliveira de Azeméis	5 (15.2%)
- Vale de Cambra	2 (6.1%)
- São João da Madeira	1 (3.0%)
- Arouca	1 (3.0%)
- Ílhavo	1 (3.0%)
Preadmission comorbidities	
- Dyslipidemia	18 (54.5%)
- Arterial hypertension	14 (42.4%)
- Uncomplicated diabetes mellitus	11 (33.3%)
- History of myocardial infarction	4 (12.1%)
- Current smoker	2 (6.1%)
- Congestive heart failure	2 (6.1%)
- Cerebrovascular disease	2 (6.1%)
- Peripheral artery disease	1 (3.0%)
- Chronic pulmonary disease	1 (3.0%)
- Uncomplicated chronic liver failure	1 (3.0%)
- Active cancer	1 (3.0%)
- At least one comorbidity	29 (87.9%)
- Age-adjusted CCI estimated 10-year survival (%), median (IQR)	77.5 (36.8)
Presenting symptoms	
- Cough	29 (87.9%)
- Fever	24 (72.7%)
- Dyspnea	17 (51.5%)
- Sputum	5 (15.2%)
- Diarrhea	5 (15.2%)
- Myalgia/fatigue	4 (12.1%)
- Nausea/emesis	3 (9.1%)
- Anosmia	2 (6.1%)
Origin of admission	
- General ward	20 (60.6%)
- Emergency Department	13 (39.4%)

Legend: COVID-19=Coronavirus disease 2019; SD=standard deviation; CCI=Charlson Comorbidity Index; IQR=interquartile range.

Table 2. Clinical course of mechanically ventilated patients with COVID-19

	All (n=33)
SOFA score on the first 24h of ICU stay (n), median (IQR)	7 (2)
Time from symptom onset to hospital admission (days), median (IQR)	6 (7)
Time from symptom onset to ICU admission (days), median (IQR)	9 (7)
Time from hospital admission to ICU admission (hours), median (IQR)	41.0 (71.0)
Length of stay[a] (days), median (IQR)	11.3 (6.9)
Duration of mechanical ventilation (days), median (IQR)	9.5 (8.1)
Tracheostomy, n (%)	3 (9.1%)
Renal replacement therapy, n (%)	1 (3.0%)
Veno-venous extracorporeal membrane oxygenation, n (%)	1 (3.0%)
Intravenous antibiotics, n (%)	28 (84.8%)
Systemic glucocorticoids, n (%) - Time from ICU admission to glucocorticoids initiation (days), median (IQR)	13 (39.4%) 6.8 (8.1)
Follow up on day 28 after ICU admission - Hospital discharge, n (%) - Post acute care facility, n (%) - Deceased, n (%) - ICU, n (%)[b] - Internal Medicine General Ward, n (%)	 18 (54.5%) 7 (21.2%) 4 (12.1%) 3 (9.1%) 1 (3.0%)

Legend: COVID-19=Coronavirus disease 2019; SOFA=Sequential Organ Failure Assessment; ICU=intensive care unit; IQR=interquartile range.
[a]Length of stay begins with admission time and ends with discharge time or time of death in the ICU.
[b]Including one patient successfully decannulated from veno-venous extracorporeal membrane oxygenation.

Table 3. Presenting features of mechanically ventilated patients with COVID-19 on ICU admission

	All (n=33)	Survivors (n=29)	Non-survivors (n=4)	p value
Laboratory results				
- Hemoglobin (g/dl), mean (SD)	12.9 (0.3)			
- Leukocytes (x 10^6/l), mean (SD)	7615.2 (568.8)			
- Lymphocytes (x 10^6/l), median (IQR)	790 (670)			
- Platelets (x 10^6/l), median (IQR)	209,000 (87,000)			
- AST (IU/l[a]), median (IQR)	39.5 (37)			
- ALT (IU/l[a]), median (IQR)	34 (47)			
- GGT (IU/l[b]), median (IQR)	69 (119)			
- Total bilirubin (mg/dl[a]), median (IQR)	0.60 (0.42)			
- INR[c], median (IQR)	1.2 (0.2)			
- Albumin (g/dl[d]), mean (SD)	3.4 (0.1)			
Last ABG on spontaneous breathing (before ET)				
- pH[a], median (IQR)	7.46 (0.06)			
- PaO2/FiO2 ratio (mmHg[a]), mean (SD)	165.0 (9.7)	174.1 (9.5) [a]	101.3 (22.5)	0.01
- Partial CO2 pressure (mmHg[a]), median (IQR)	38.5 (10.0)			
- Bicarbonate (mmol/l[c]), mean (SD)	26.8 (0.8)			
- Lactate (mmol/l[e]), median (IQR)	1.0 (0.5)			
SAPS II (n), median (IQR)	33.0 (17)	32.0 (11.0)	48.5 (14.0)	0.004

Legend: COVID-19=Coronavirus disease 2019; ICU=intensive care unit; SD=standard deviation; IQR=interquartile range; AST=aspartate transaminase; ALT=alanine aminotransferase; GGT=gamma glutamyl transferase; INR=international normalized ratio; ABG=arterial blood gas; ET=endotracheal intubation; PaO2=arterial oxygen partial pressure; FiO2=fractional inspired oxygen; CO2=carbon dioxide; SAPS II=Simplified Acute Physiology Score II.
[a]Data missing for 1 patient.
[b]Data missing for 6 patients.
[c]Data missing for 2 patients.
[d]Data missing for 7 patients.
[e]Data missing for 3 patients.

Table 4. Ventilatory parameters from day 1 to day 5 of ICU stay

	All (n=33)	Survivors (n=29)	Non-survivors (n=4)	p value
Prone positioning				
- Number of patients, n (%)	30 (90.9%)			
- Number of sessions (n), median (IQR)	3.0 (3.0)	3.0 (4.0)	4.0 (1.0)	0.318
PaO2/FiO2 ratio (mmHg), mean (SD)				
- Day 1	134.9 (6.2)	140.9 (6.0)	91.5 (15.9)	0.008
- Day 2	154.6 (7.8)	159.9 (8.1)	115.8 (17.0)	0.062
- Day 3	161.5 (10.4)	168.9 (11.1)	107.8 (5.7)	<0.001
- Day 4[a]	159.7 (10.7)	166.6 (11.6)	111.0 (13.1)	0.086
- Day 5[b]	171.3 (10.8)	179.1 (11.3)	121.0 (22.1)	0.066
Tidal volume (ml/kg IBW), median (min/max)				
- Day 1[c]	6.5 (4.8/9.1)	6.4 (4.8/9.1)	6.6 (6.2/7.4)	0.771
- Day 2[d]	6.7 (5.7/8.3)	6.6 (5.7/8.3)	6.9 (6.2/7.4)	0.678
- Day 3[e]	6.6 (5.7/8.2)	6.6 (5.7/8.2)	6.6 (6.0/7.4)	0.890
- Day 4[f]	6.8 (5.7/8.9)	6.7 (5.7/8.9)	6.8 (6.2/7.0)	0.872
- Day 5[g]	6.9 (6.0/10.3)	7.0 (6.0/10.3)	6.5 (6.2/6.9)	0.294
PEEP (cmH2O), median (IQR)				
- Day 1	10.0 (2.0)	11.0 (2.0)	9.0 (8.0)	0.270
- Day 2[c]	10.0 (3.0)	10.0 (3.0)	13.0 (5.0)	0.117
- Day 3[h]	10.0 (4.0)	10.0 (4.0)	10.0 (7.0)	0.854
- Day 4[i]	10.0 (4.0)	10.0 (4.0)	11.0 (5.0)	0.393
- Day 5[j]	10.5 (3.0)	10.0 (4.0)	13.0 (4.0)	0.073
Driving pressure (cmH2O), median (IQR)				
- Day 1[k]	11.0 (5.0)	11.0 (6.0)	12.0 (4.0)	0.761
- Day 2[c]	12.0 (4.0)	12.0 (3.0)	13.5 (5.0)	0.342
- Day 3[h]	12.0 (3.0)	12.0 (3.0)	12.0 (2.0)	0.368
- Day 4[i]	13.0 (2.0)	13.0 (3.0)	12.0 (2.0)	0.652
- Day 5[j]	12.0 (3.0)	12.0 (3.0)	12.5 (3.0)	0.886

Static compliance (ml/cmH2O), median (IQR)				
- Day 1[k]	39.0 (16.0)	40.0 (16.0)	39.0 (*)	0.580
- Day 2[l]	35.0 (9.0)	35.0 (9.0)	37.5 (13.0)	0.615
- Day 3[h]	36.0 (8.0)	36.0 (5.0)	46.5 (11.0)	0.071
- Day 4[i]	38.0 (13.0)	38.0 (12.0)	42.5 (10.0)	0.204
- Day 5[j]	40.5 (14.0)	40.0 (14.0)	43.5 (14.0)	0.669

Legend: ICU=intensive care unit; IQR=interquartile range; PaO2=arterial oxygen partial pressure; FiO2=fractional inspired oxygen; SD=standard deviation; IBW=ideal body weight; min=minimum; max=maximum.
[a]Data missing for 1 patient (successfully extubated).
[b]Data missing for 3 patients (2 successfully extubated, 1 transferred to extracorporeal membrane oxygenation [ECMO] center).
[c]Data missing for 1 patient (true missing - survivor).
[d]Data missing for 3 patients (true missing - 1 survivor, 2 non-survivors).
[e]Data missing for 3 patients (2 successfully extubated, 1 true missing - non-survivor).
[f]Data missing for 7 patients (5 successfully extubated, 1 transferred to ECMO center, 1 true missing - non-survivor).
[g]Data missing for 8 patients (6 successfully extubated, 1 transferred to ECMO center, 1 true missing - non-survivor).
[h]Data missing for 2 patients (successfully extubated).
[i]Data missing for 6 patients (5 successfully extubated, 1 transferred to ECMO center).
[j]Data missing for 7 patients (6 successfully extubated, 1 transferred to ECMO center).
[k]Data missing for 2 patients (true missing, 1 survivor, 1 non-survivor).
[l]Data missing for 2 patients (true missing, 2 survivors).
*Impossible to compute IQR, minimum 32.0/maximum 63.0.

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