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An appraisal of respiratory system compliance in mechanically ventilated covid-19 patients

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Abstract

Background: Heterogeneous respiratory system static compliance (C_{RS}) values and levels of hypoxemia in patients with novel coronavirus disease (COVID-19) requiring mechanical ventilation have been reported in previous small-case series or studies conducted at a national level.

Methods: We designed a retrospective observational cohort study with rapid data gathering from the international COVID-19 Critical Care Consortium study to comprehensively describe C_{RS}—calculated as: tidal volume/[airway plateau pressure-positive end-expiratory pressure (PEEP)]—and its association with ventilatory management and outcomes of COVID-19 patients on mechanical ventilation (MV), admitted to intensive care units (ICU) worldwide.

Results: We studied 745 patients from 22 countries, who required admission to the ICU and MV from January 14 to December 31, 2020, and presented at least one value of C_{RS} within the first seven days of MV. Median (IQR) age was 62 (52–71), patients were predominantly males (68%) and from Europe/North and South America (88%). C_{RS}, within 48 h from endotracheal intubation, was available in 649 patients and was neither associated with the duration from onset of symptoms to commencement of MV ($p = 0.417$) nor with PaO_2/FiO_2 ($p = 0.100$). Females presented lower C_{RS} than males (95% CI of C_{RS} difference between females-males: − 11.8 to − 7.4 mL/cmH_2O $p < 0.001$), and although females presented higher body mass index (BMI), association of BMI with C_{RS} was marginal ($p = 0.139$). Ventilatory management varied across C_{RS} range, resulting in a significant association between C_{RS} and driving pressure (estimated decrease − 0.31 cmH_2O/L per mL/cm$H_2$0 of C_{RS}, 95% CI − 0.48 to − 0.14, $p < 0.001$). Overall, 28-day ICU mortality, accounting for the competing risk of being discharged within the period, was 35.6% (SE 1.7). Cox proportional hazard analysis demonstrated that C_{RS} (+ 10 mL/cm H_2O) was only associated with being discharge from the ICU within 28 days (HR 1.14, 95% CI 1.02–1.28, $p = 0.018$).

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Conclusions: This multicentre report provides a comprehensive account of C_{RS} in COVID-19 patients on MV. C_{RS} measured within 48 h from commencement of MV has marginal predictive value for 28-day mortality, but was associated with being discharged from ICU within the same period. Trial documentation: Available at https://www.covid-critical.com/study.

Trial registration: ACTRN12620000421932.

Keywords: Mechanical ventilation, Compliance, ARDS, COVID-19, SARS-CoV-2

Background

Millions of people have been infected by SARS-CoV-2 worldwide, and many of those have been hospitalized for respiratory complications associated with coronavirus disease-2019 (COVID-19). Many of those COVID-19 hospitalised patients have received mechanical ventilation (MV), due to the development of acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) [1–4]. To date, several landmark studies [5–8] have improved our understanding of COVID-19 pulmonary pathophysiology, but pulmonary derangement in COVID-19 and appropriate ventilatory management remains incompletely characterized.

Earlier reports on the pulmonary pathophysiology of COVID-19 patients reported conflicting results and extreme heterogeneity in levels of pulmonary shunting, static respiratory system compliance (C_{RS}), [9–12] and substantial heterogeneity in lung recruitability [13, 14]. Adding further to the controversy over C_{RS} in COVID-19 patients, Grasselli and collaborators [7] have compared findings from an Italian repository of COVID-19 ARDS with previous ARDS cases of different etiologies. They found statistically significant higher C_{RS} in patients with COVID-19 ARDS. In addition, they found that patients who presented with lower C_{RS} and higher D-dimer values had the greatest mortality risk. In line with these figures, in a small-case series, Chiumello and collaborators found that COVID-19 patients presented higher C_{RS} levels in comparison with patients with ARDS from other etiologies and matched levels of hypoxemia [12]. Regrettably, those previous reports did not provide any information on how C_{RS} progressed beyond a punctual assessment during the period of MV. In contrast, in another landmark study by Ferrando et al. [6], C_{RS} figures from a Spanish database were very similar to previously published cohorts of ARDS patients. The authors also found that intensive care unit (ICU) discharge and mortality were not influenced by the initial levels of C_{RS}.

In a pandemic caused by a novel virus, access to international data is vital, because it may help account for differences in populations, access to medical care, equipment and critical variations in clinical managements among countries. Thus, analysis of international repositories improves the overall understanding of a novel disease and helps establishing best practices to enhance outcome. One example of how single-center or single-country studies can influence medical care early in a pandemic, before being contradicted by subsequent international findings is the issue of C_{RS}. Indeed, as this parameter can be markedly impacted by fine variations in ventilatory management, extrapolations from monocenter or single-country studies may be challenging. In early January 2020, the COVID-19 Critical Care Consortium incorporating the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (COVID-19–CCC/ECMOCARD) group was founded to investigate patients presenting to ICUs worldwide.

Here, we present a comprehensive appraisal of C_{RS} in mechanically ventilated COVID-19 patients enrolled into the COVID-19–CCC/ECMOCARD international study, in order to understand the dynamics of C_{RS} during the first week of mechanical ventilation and its potential impact on patient outcomes.

Materials and methods

Study design and oversight

The COVID-19-CCC/ECMOCARD is an international, multicentre, cohort observational study ongoing in 351 hospitals across 53 countries. The full study protocol is available elsewhere [15]. To summarize, participating hospitals obtained local ethics committee approval and a waiver of informed consent was granted in all cases. ISARIC/SPRINT-SARI data collection began at admission to hospital, while data collection for the COVID-19–CCC observational study commenced at admission to the ICU. De-identified patient data were collected retrospectively and stored via the REDCap electronic data capture tool, hosted at the University of Oxford, United Kingdom or Monash University, Melbourne, Australia.

Study population

We reviewed data of all patients admitted to the ICU at a COVID-19–CCC collaborating site, from January 14 through September 30, 2020, with a clinically suspected or laboratory confirmed diagnosis of SARS-CoV-2 infection, through naso-pharyngeal swab for real-time PCR SARS-CoV-2 detection. Of note, suspicion

of SARS-CoV-2 infection was based on symptoms and onset of infection and was confirmed by the clinician when COVID-19 infection was the most likely cause of the symptoms experienced. Patients excluded were those under the age of 15 years or admitted to an ICU for other reasons. We focused our analysis on patients on controlled MV and with a computed C_{RS} value within 48 h of MV commencement.

Definitions and pulmonary mechanics computations

C_{RS} was calculated as: tidal volume (mL)/[(airway plateau pressure-PEEP (cmH_2O))]. Of note, we provided to data collectors a detailed data dictionary, with instructions on how to collect airway plateau pressure values, via an inspiratory pause of approximately 3 s. We computed C_{RS} using the first measured tidal volume, airway plateau pressure and PEEP values, within 48 h of MV commencement. In the sub-population of patients on controlled MV, without ECMO support, we analysed key pulmonary variables, such as tidal volume, positive end expiratory pressure (PEEP), static driving pressure, inspiratory fraction of oxygen (FiO_2), and gas exchange, recorded during routine clinical practice and only. Tidal volume was reported in mL/kg of predicted body weight (PBW) [16].

Data collection

After enrolment, data on demographics, comorbidities, clinical symptoms and laboratory results were collected by clinical and research staff of the participating ICUs in an electronic case report form [15]. Details of respiratory and hemodynamic support, physiological variables, and laboratory results were collected daily. Of note, the worst daily values were preferentially recorded. The duration of MV and ICU stay, and hospital mortality were recorded. Analysis of daily data was restricted to the first seven days from commencement of MV.

Statistical analyses

Descriptive statistics summarised demographics, clinical signs on ICU admission, ICU management and clinical outcomes for the overall study cohort and subjects with baseline compliance measured within the first 48 h of controlled MV. Statistics were reported as medians (interquartile range) for continuous variables and numbers (percentage) for categorical variables. Linear regression was applied to summarise associations between baseline compliance with body mass index (BMI) (including interaction between BMI and sex), days from symptom onset to MV commencement and PaO_2/FiO_2, adjusted for BMI. Linear mixed modelling was used to investigate trends in compliance over time and associations with key respiratory parameters during the first 7 days of controlled MV. Models assumed a linear effect for days and a random intercept per subject to account for repeated measures. Consistent with exploratory analyses, BMI was included as a fixed effect to adjust for potential confounding in the clinical characteristics and management of patients with different BMI. Hypothesis testing was applied to all fixed effects, assuming a 5% level of statistical significance. Results were summarised graphically with uncertainty in estimated trends represented by 95% prediction intervals. Expected patient outcomes including length of ICU stay, duration of MV and risk of ICU mortality versus discharge were examined using multi-state modelling [17]. Compared with exploratory analyses of clinical outcomes, the multistate model accounted for ICU discharge and death as competing events and allowed data from all patients to be included, regardless of study follow-up time. The model comprised of four states, to describe patients prior to commencement of MV (non MV), on mechanical ventilation (MV), ICU discharged (Discharge) and mortality (Death). States were presented as percentage and standard error (SE) in the text. Patients extubated before death or discharge were assumed to transition between MV an non-MV states. State transitions were modelled by Cox proportional hazards, with patients censored at last known follow-up, up to 28 days from ICU admission. Follow-up analysis considered Cox proportional hazard regression to examine associations between baseline compliance and competing risks of ICU mortality and discharge, following commencement of MV. Baseline compliance was included as a linear effect, with age, sex, BMI and comorbidities (hypertension, chronic cardiac disease, chronic kidney disease) as additional covariates and adjusted for recruiting centre. A shared frailty term (Gamma distributed) was included to account for residual variation between study sites. Analyses were conducted using R version 3.6.2 or higher (The R Foundation).

Results

We studied 745 patients from 22 countries, who required admission to the ICU and MV from January 14 to December 31, 2020, and presented at least one value of C_{RS} within the first seven days of MV. Among those, 597 (80%) had laboratory-confirmed diagnosis of SARS-CoV2 infection, while in 148 (20%), infection was clinically suspected. Enrolment rate, since January 2020, is reported in Fig. 1. C_{RS}, within 48 h from endotracheal intubation, was available in 649 patients (Fig. 2). No association between C_{RS} and days from onset of symptoms to commencement of MV was found (Fig. 3). Median C_{RS} (IQR), within the first 48 h of mechanical ventilation, was 34.1 mL/cmH_2O (26.4–44.0) and PaO_2/FiO_2 113.0 mmHg (84.0–161.3), without any linear association between these parameters. In particular, 16%, 46% and 38% of the patients presented

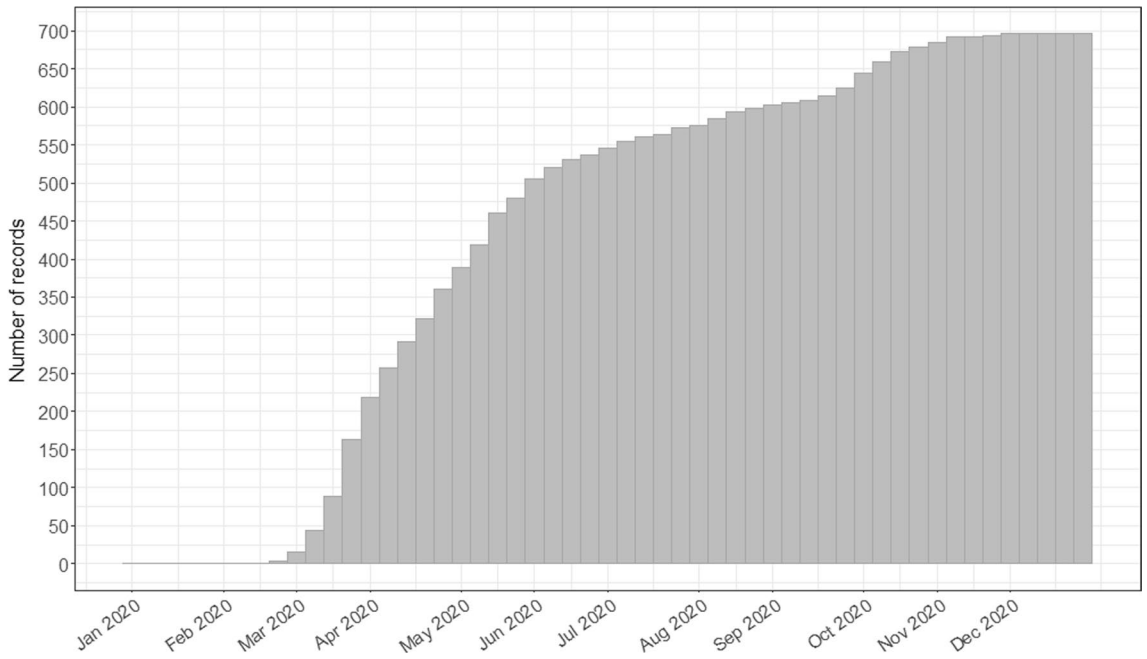


Fig. 1 Patient enrolment rate from January 14 through December 31, 2020

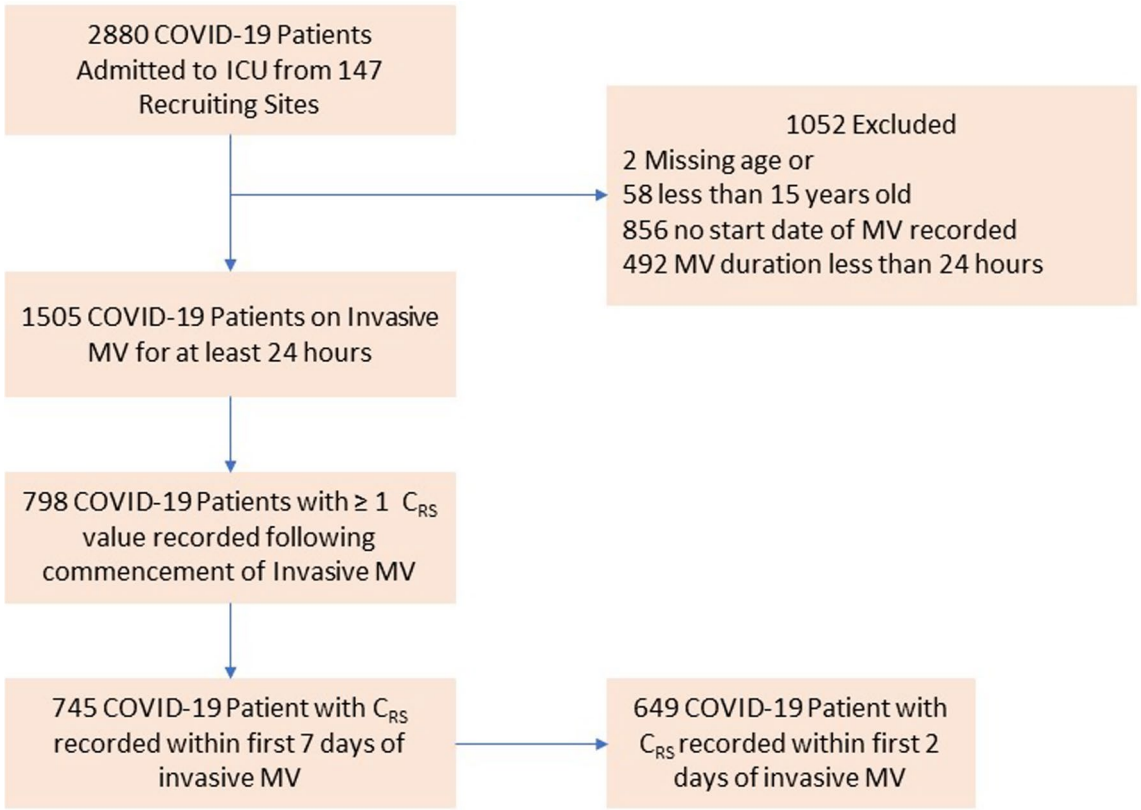


Fig. 2 Patient population flow chart. The analysis of 1505 COVID-19 patients on mechanical ventilation identified 649 patients with static respiratory system compliance within 48 h from commencement of mechanical ventilation

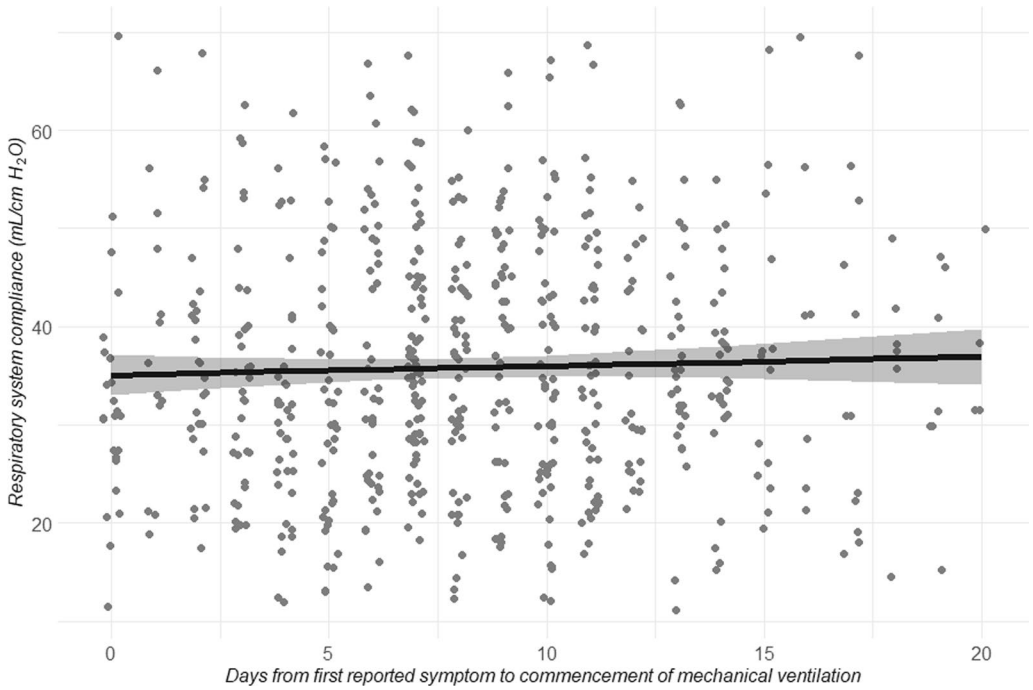


Fig. 3 Linear regression analysis of days from onset of symptoms to commencement of mechanical ventilation and static respiratory system compliance, based on the first measurement obtained within 48 h from commencement of mechanical ventilation, adjusted for body mass index. Dark black horizontal bar depicts median value, and upper and lower horizontal light black bars show 90th and 10th percentile. Days of onset of symptoms to commencement of mechanical ventilation was not associated with static respiratory system compliance (estimate 0.92 mL/cmH_2O, 95% CI −0.31–0.31 $p=0.417$)

with mild, moderate or severe hypoxemia, respectively (Fig. 4a). Female sex was associated with a significantly lower C_{RS} than in males (95% CI of difference between genders: −11.8 to −7.4 mL/cmH_2O $p<0.001$) (Fig. 4b). Females also presented higher body mass index (BMI) (95% CI of difference between males and females: −1.9 to −5.5, $p<0.001$), but as shown in Fig. 5, C_{RS} and BMI were not linearly associated. Our model estimated that C_{RS} was 37.57 cmH_2O/mL (95% CI 36.5–38.6) upon commencement of MV (Fig. 6), with further worsening in the first seven days of MV (estimated decrease −0.31 cmH_2O/mL per day, 95% CI −0.48 to −0.14, $p<0.001$). In addition, as detailed in Fig. 7, $PaCO_2$, tidal volume, PEEP, driving pressure and FiO_2 significantly varied across the range of C_{RS}, and a significant association was found between inspiratory plateau pressure and C_{RS} changes (Fig. 8).

Baseline characteristics upon ICU admission, applied interventions and outcomes, are summarized in Table 1. The most common interventions applied to the study population were use of antibiotics (96%), neuromuscular blocking agents (81%) and prone position (61%). The overall hospital mortality of the study population was 40%, and among those patients who died in the hospital or were discharged alive, the median (IQR) duration of MV was 11 days (6–18) and 14 days (8–23), respectively. Overall, 28-day ICU mortality, accounting for competing risks, was 35.6% (SE 1.7) and estimated 28-day mortality from commencement of MV was 37.1% (SE 1.7) (Fig. 9b). Cox proportional hazard analysis (Fig. 9c) demonstrated that age (hazard ratio 1.37, 95% CI 1.19–1.59, $p<0.001$) and chronic cardiac diseases (HR 1.62, 95% CI 1.14–2.29, $p<0.001$) were the only baseline factors associated with 28-day mortality risk. In addition, age (HR 0.77, 95% CI 0.66–0.83, $p<0.001$), male sex (HR 0.59, 95% CI 0.44–0.79, $p<0.001$), BMI (HR 0.86, 95% CI 0.79–0.95, $p=0.003$) and C_{RS} (+10 mL/cm H_2O) (HR 1.14, 95% CI 1.02–1.28, $p=0.018$) were associated with the chance of being discharge from the ICU within 28 days.

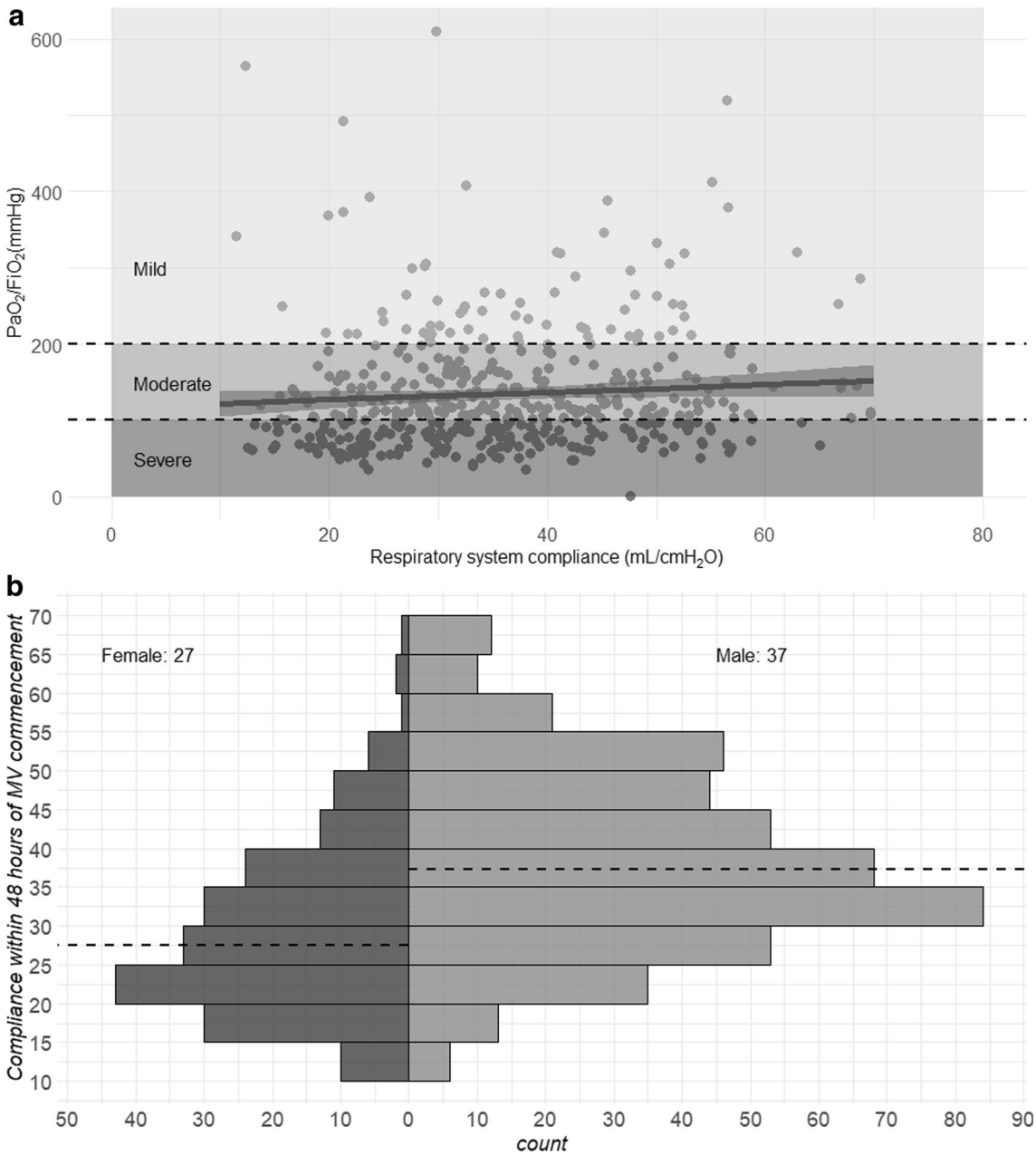


Fig. 4 **a** Linear regression analysis of arterial partial pressure of oxygen (PaO_2/FiO_2) and respiratory system compliance (C_{RS}), based on the first measurement obtained within 48 h from commencement of mechanical ventilation, with an interaction of gender and adjusted for body mass index (BMI). No statistically significant association was found between PaO_2/FiO_2 and C_{RS} (estimate 0.49, 95% CI −0.09–1.07 $p=0.100$). Typical acute respiratory distress syndrome stratification groups [35] (severe, moderate and mild based on levels of hypoxemia) are highlighted in dark, medium and light grey, respectively. **b** Static respiratory system compliance (C_{RS}) distribution by sex, based on the first measurement obtained within 48 h from commencement of mechanical ventilation. Dashed black lines depict median values for females and males

Discussion

This large observational report from intensive care units throughout the world found that initial static respiratory system compliance was only associated with hazard of being discharged from the ICU within 28 days. The duration from onset of symptoms to commencement of MV did not influence C_{RS}, and interestingly lower C_{RS} was found in female patients. In the evaluated population, neuromuscular blocking agents and prone position were commonly applied and ventilatory management

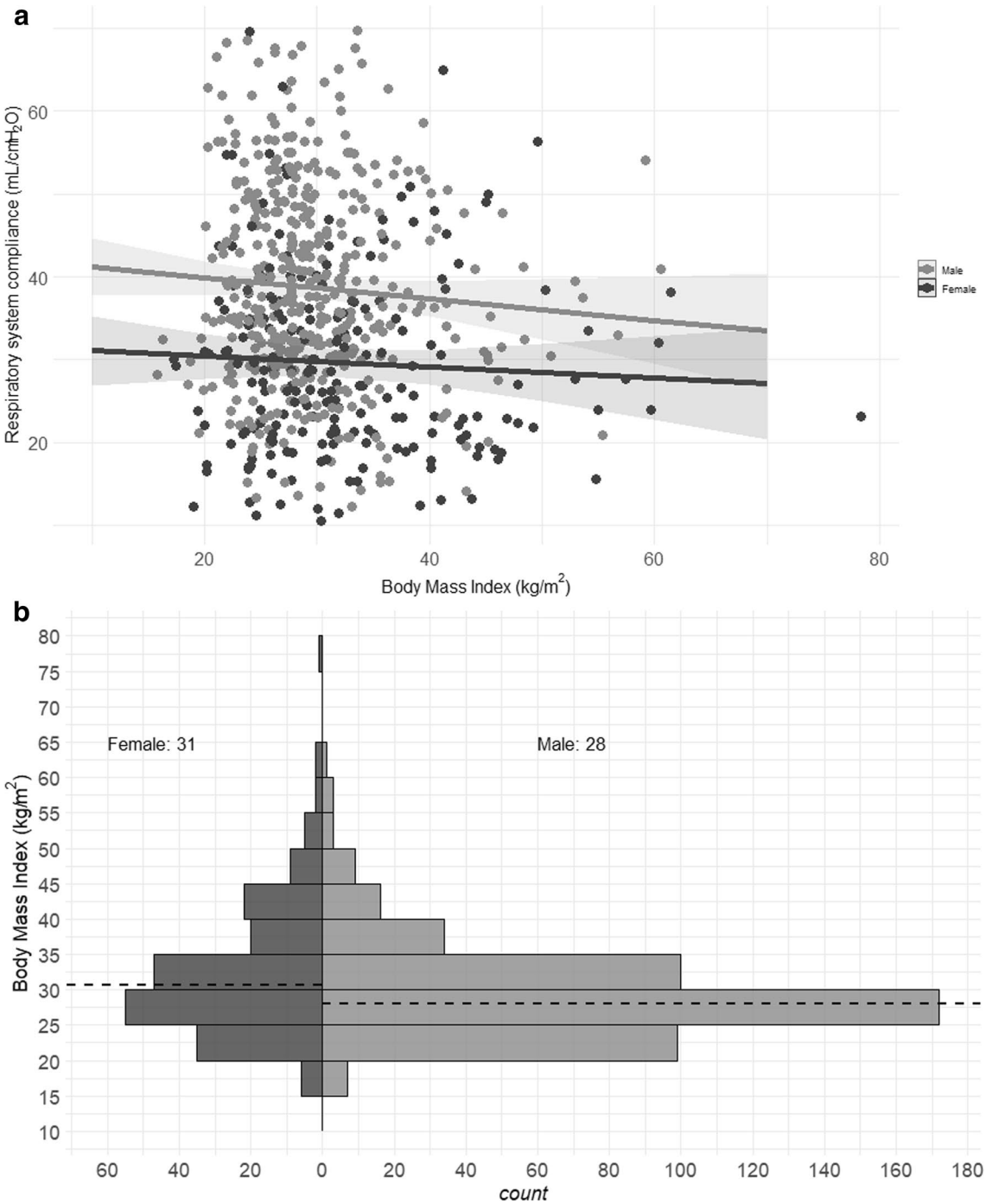


Fig. 5 Linear regression analysis of static respiratory system compliance, based on the first measurement obtained within 48 h from commencement of mechanical ventilation, and body mass index with an interaction for sex. Per each graph, fitted line of the model is depicted and the upper and lower lines display the 95% predictive interval. Dark grey dots depict female patients, while light grey dots males. Static respiratory system compliance did not vary according to the body mass index (estimate − 0.12 cmH_2O/mL, 95%CI − 0.29 to − 0.04, $p = 0.139$), but was associated with female sex (estimate − 10.73 cmH_2O/mL, 95%CI − 18.54 to − 2.92, $p = 0.007$)

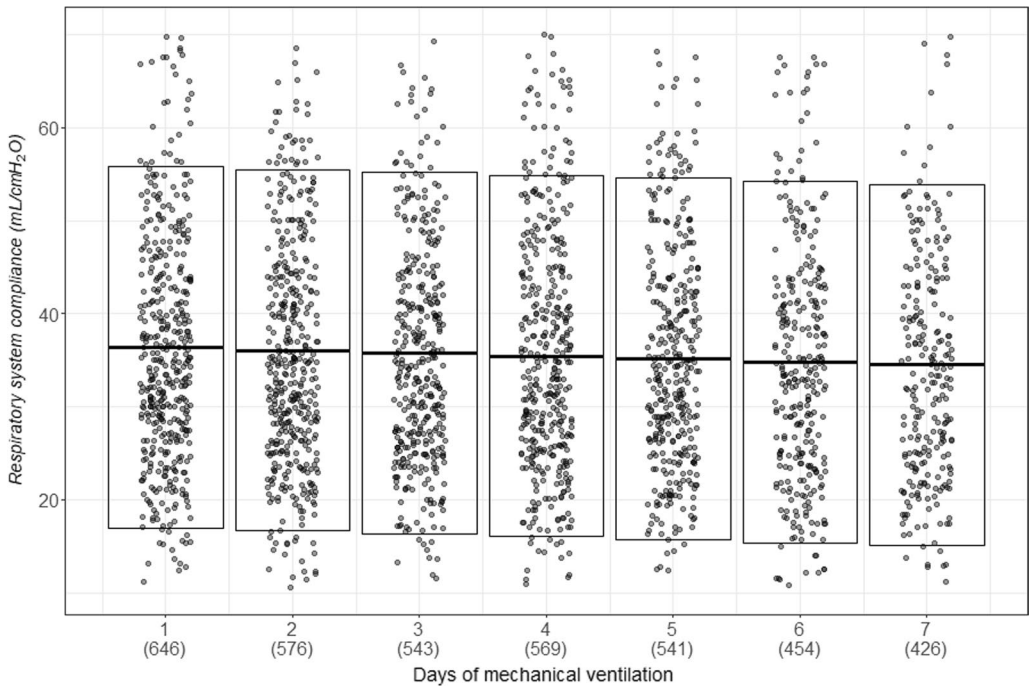


Fig. 6 Static respiratory system compliance dynamics. Evolution of static respiratory system compliance over the first 7 days of mechanical ventilation, adjusted for body mass index. Under each day, the number of analysed patients is reported in parenthesis. Fitted line of the model is depicted, and the upper and lower lines display the 95% predictive interval. Respiratory system compliance varied during the first seven days of mechanical ventilation (estimate −0.31 cmH_2O/mL, 95%CI −0.48 to 0.14, $p < 0.001$)

across C_{RS} levels varied in terms of tidal volume, PEEP and FiO_2, throughout the first 7 days of MV.

In comparison with previous reports on ARDS patients without COVID-19 [18], we similarly found that the majority of patients exhibited moderate hypoxemia, even when presented higher C_{RS}. We also noted a larger range of C_{RS} in line with previous studies [7, 8], but in contrast with values from a larger COVID-19 ARDS series from Spain [6]. Considering that we focused our analysis on static compliance of the respiratory system, without partitioning into the pulmonary and chest wall components [19, 20], it is interesting that C_{RS} was not associated with BMI, suggesting that patients with higher BMI potentially presented also with higher lung compliance. Irrespective, we found lower C_{RS} in female patients, who also presented higher BMIs. To the best of our knowledge, no studies have systematically investigated the effects of gender/BMI on COVID-19 severity; thus, whether obesity might be a crucial risk factor for ICU admission and mechanical ventilation, specifically in female patients, and its effects on lung compliance should be further explored. We also found that throughout the range of C_{RS} values, plateau pressure was within what is typically presumed as lung protective ranges [21], but this resulted in potentially harmful driving pressures, specifically for patients with the lowest C_{RS} values. As many of these patients were obese, this raises the question of whether these modest pressures might have increased the risk of pulmonary derecruitment, or in patients with normal BMI, the resulting driving pressure might have been related to pulmonary overdistention. These factors could have contributed to sustained hypoxemia and impaired lung function throughout the study period. In such circumstances, it is questionable whether MV guided by oesophageal pressure monitoring may have some benefits [22], but more research is needed to corroborate such reasoning.

Phenotypic subsets of COVID-19-associated ARDS have been proposed [9, 13, 23–25]. Recent study has also explored whether C_{RS}—related phenotype patterns existed among patients with ARDS before the COVID-19 pandemic [26]. Various investigators [7, 27], who did not find significant C_{RS} variability among COVID-19 patients requiring MV, questioned the overall clinical value of C_{RS} in the COVID-19 population. In a very small case series, Gattinoni et al [9] found an initial C_{RS} of 50 mL/cmH_2O, but high levels of shunt fraction that could have explained the resulting severe hypoxemia. In subsequent study, Chiumello and collaborators found higher C_{RS} in patient with COVID-19 ARDS and ARDS caused by

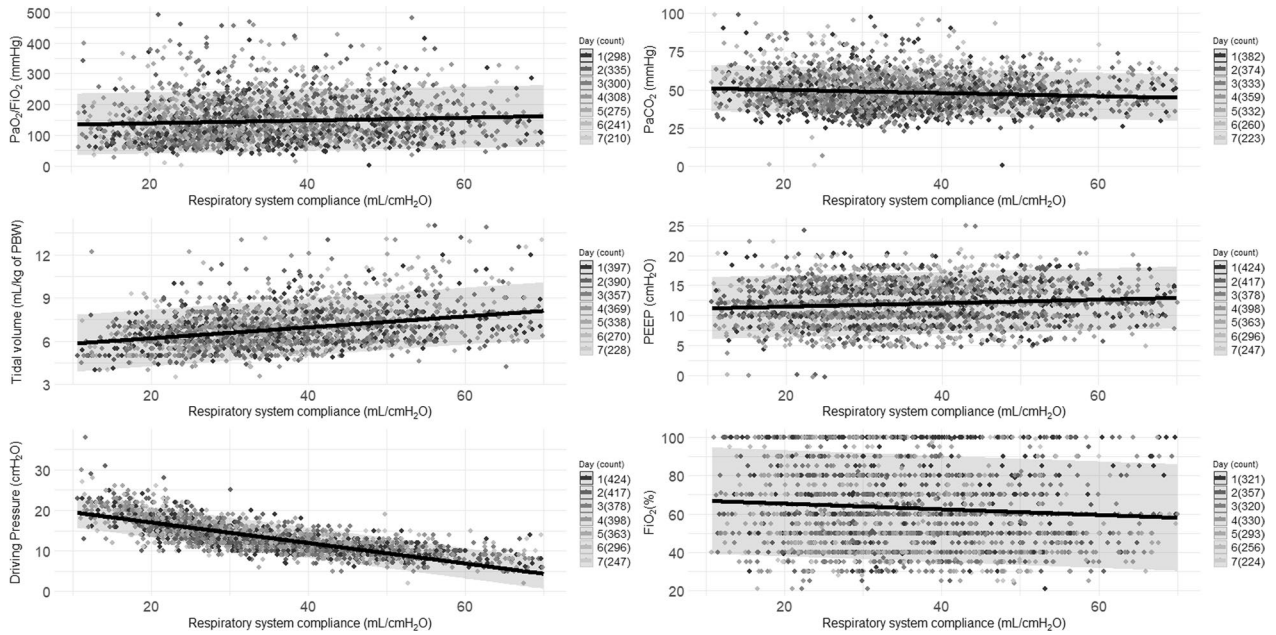


Fig. 7 Linear Mixed model analysis of respiratory system compliance vs. crucial pulmonary variables during the first 7 days of mechanical ventilation (grey-scale coded bar for day 1 through 7 is reported on the right section of each graph and in parenthesis is reported the number of analysed patients). Per each graph, fitted line of the model is depicted and the upper and lower lines display the 95% predictive interval. All analyses are adjusted for body mass index. Static compliance of respiratory system was found to be associated with $PaCO_2$ (estimated decrease −0.11 mmHg, 95% CI −0.15 to −0.06, $p < 0.001$), tidal volume (estimated increase 0.04 mL/Kg of predicted body weight per day, 95% CI 0.03–0.04, $p < 0.001$), PEEP (estimated increase −0.03 cmH_2O, 95% CI 0.02–0.04, $p < 0.001$), driving pressure (estimated decrease −0.31 cmH_2O/L, 95% CI −0.48 to 0.14, $p < 0.001$) and FiO_2 (estimated decrease −0.15%, 95% CI −0.23 to −0.06, $p < 0.001$). While PaO_2/FiO_2, was not significantly associated with static compliance of respiratory system (estimated increase 0.29 mmHg, 95% CI −0.03 to 0.61, $p = 072$) PaO_2/FiO_2, ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen; $PaCO_2$ arterial partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure

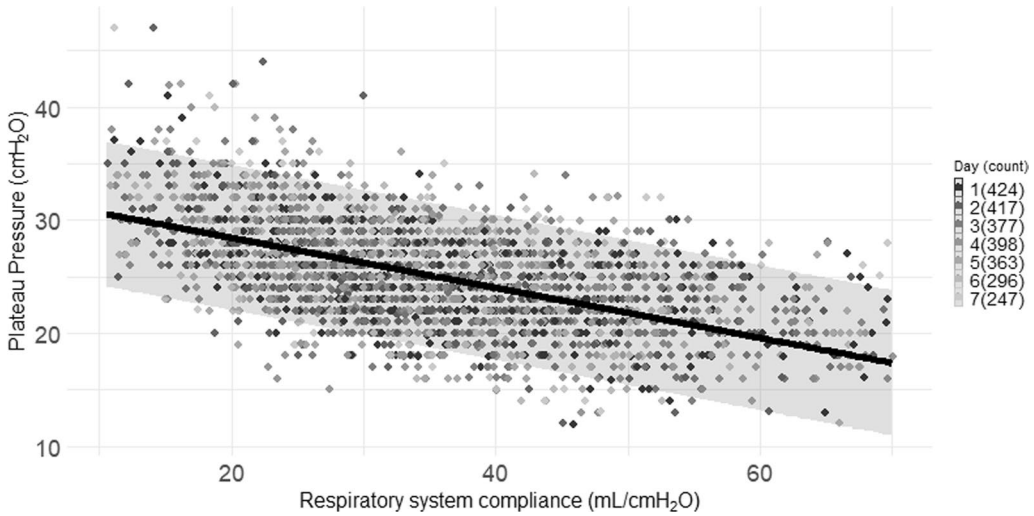


Fig. 8 Association of airway inspiratory plateau pressure with static respiratory system compliance. Linear Mixed model analysis of the association of respiratory system compliance with airway inspiratory plateau pressure during the first 7 days of mechanical ventilation (grey-scale coded bar for day 1 through 7 is reported on the right section of each graph and in parenthesis is reported the number of analysed patients). Fitted line of the model is depicted, and the upper and lower lines display the 95% predictive interval. Analysis is adjusted for body mass index. The model highlights significant association between respiratory system compliance and airway plateau pressure (estimated decrease −0.22 cmH_2O/L, 95% CI −0.23 to −0.21, $p < 0.001$), but based on the model prediction, airway plateau pressure remained predominantly below 30 cmH_2O

Table 1 Only patients with the following characteristics were included in this analysis: (1) on controlled mechanical ventilation; (2) airway plateau pressure, tidal volume and positive-end-expiratory pressure recorded within 48 h from commencement of mechanical ventilation

Characteristic	Full cohort ($n = 745$)	First C_{RS} recorded within 48 hr of MV ($n = 649$)
Age, years: *n*; median (IQR)	745; 62 (52–71)	649; 62 (53–71)
Male: *n* (%)	510 (68)	445 (69)
Geographic region: *n* (%)		
Africa	19 (3)	14 (2)
Asia	63 (8)	57 (9)
Australia and New Zealand	6 (1)	4 (1)
Europe	326 (44)	295 (45)
Latin America and the Caribbean	108 (14)	92 (14)
Northern America	223 (30)	187 (29)
Time from onset of symptoms, days: *n*; median (IQR)		
Onset of symptoms to hospital admission	735; 7 (3–9)	643; 7 (3–9)
Onset of symptoms to ICU admission	735; 7 (5–11)	643; 7 (5–11)
Onset symptoms to mechanical ventilation	735; 8 (5–11)	643; 8 (5–11)
Clinical signs on ICU admission: *n*; median (IQR)		
WBC count, 10^3/μL	604; 8.9 (6.3–12.8)	540; 9.0 (6.6–13.0)
Lymphocyte count, 10^3	459; 0.7 (0.5–1.1)	402; 0.7 (0.5–1.1)
Temperature, °C	329; 37.4 (36.5–38.1)	293; 37.4 (36.5–38.2)
Creatinine, mg/dL	613; 1.0 (0.7–1.4)	543; 1.0 (0.7–1.4)
CRP, mg/dL	216; 118.1 (29.4–206.7)	194;121 (29.1–205.6)
Lymphocyte count to CRP ratio	167; 0.01 (0–0.03)	147; 0.01 (0–0.03)
Neutrophil to Lymphocyte ratio	414; 10.1 (5.6–16.6)	364;10.2 (5.9–16.6)
D-dimer level mg/L	237; 1.3 (0.8–4.7)	207; 1.4 (0.8–4.4)
Clinical management during first 28 days of ICU admission: *n* (%)		
Antibiotics	713 (96)	621 (96)
Antivirals	288 (50)	245 (49)
Continuous renal replacement therapy	110 (15)	92 (15)
Vasoactive drugs	411 (58)	365 (58)
Cardiac-assist devices	54 (7)	48 (7)
ECMO	72 (10)	61 (9)
Prone positioning	451 (61)	392 (60)
Inhaled nitric oxide	72 (10)	66 (10)
Neuromuscular blockade[a]	599 (81)	524 (81)
Recruitment manoeuvres	295 (40)	266 (41)
Clinical outcomes		
Outcome at study end: *n* (%)		
Died in hospital	300 (40)	266 (41)
Discharged alive	400 (54)	339 (52)
Transferred to another facility	7 (1)	7 (1)
Still in hospital/outcome not finalised	38 (5)	37 (6)
Died in hospital		
Duration of ICU stay, days: *n*; median (IQR)	300; 12 (6–20)	266; 12 (6–20)
Duration of hospital stay, days: *n*, Median (IQR)	294; 13 (7–22)	260; 14 (7–22)
Duration of MV, days: *n*; Median (IQR)	300; 11 (6–18)	266; 11 (5–18)
Died within 28 days from ICU admission: *n* (%)	258 (86)	231 (87)
Discharged alive		
Duration of ICU stay, days: *n*; median (IQR)	399; 19 (12–30)	339; 19 (11–3)

Table 1 (continued)

Characteristic	Full cohort ($n=745$)	First C_{RS} recorded within 48 hr of MV ($n=649$)
Duration of hospital stay, days: *n*; Median (IQR)	396; 30 (21–46)	336; 30 (21–45)
Duration of MV, days: *n*; Median (IQR)	400; 14 (8–23)	339; 14 (8–23)
Discharged alive within 28 days from ICU admission: *n* (%)	195 (49)	165 (49)

Percentages are calculated for non-missing data

C_{RS}, static compliance of respiratory system; CRP, c-reactive protein; MV, mechanical ventilation; ICU, intensive care unit; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation

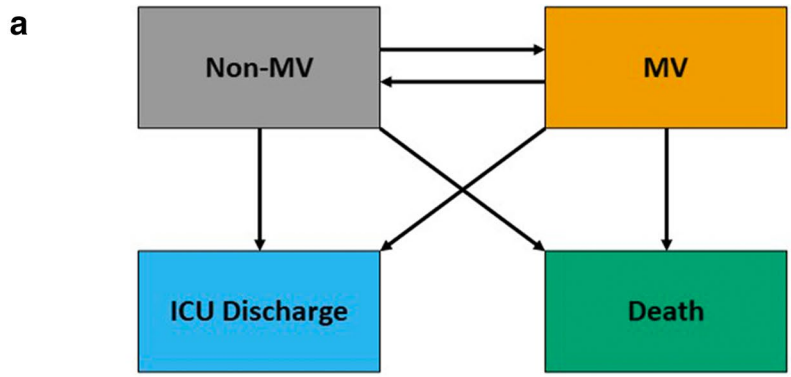
[a] Administration of neuromuscular blockade drugs administered during the first day of invasive mechanical ventilation was not included in the analysis

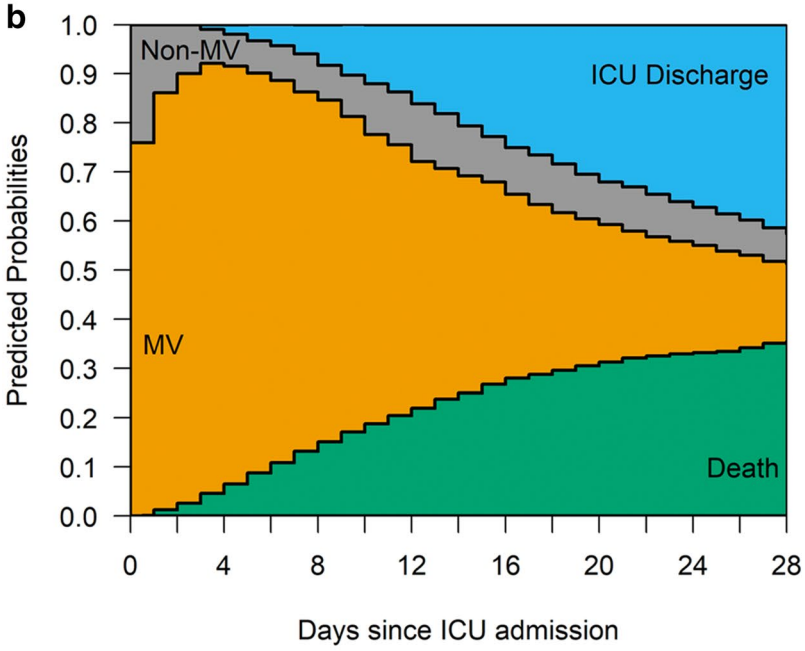
other injuries, while matching for similar levels of PaO_2/FiO_2 [12]. Interestingly, these findings were in line with computed tomography studies results, corroborating higher proportion of normally aerated tissue in COVID-19 ARDS. In similar reports, heterogeneous pathophysiology among patients with different levels of pulmonary compliance has been implied [10, 25]. As corroborated by landmark post-mortem studies [28] and clinical studies [7, 29], SARS-CoV-2 heterogeneously affects pulmonary ventilation and perfusion. Hence, it could be argued that the use of C_{RS} as key pathophysiological parameter to predict clinical evolution might be over simplistic and in-depth characterization of pulmonary pathophysiology should be recommended for COVID-19 patients, specifically when obese. Interestingly, our report is the first that specifically focused on the dynamics of C_{RS}, rather than only baseline C_{RS}. We found that C_{RS} was not related to the duration from the onset of symptoms to commencement of MV, emphasising the need for inclusive data on mechanisms of lung injury in not ventilated COVID-19 patients [30]. The median C_{RS} value found in our population was 34.1 mL/cmH_2O, similar to findings by Ferrando et al. [6], not dissimilar to findings by Bellani et al. on patients with non-COVID-19 ARDS [31], but lower than figures recently reported by Grasselli [7] and Grieco [32] in COVID-19 patients. In addition, we found a further decrease in C_{RS} during the first week of MV. This could have been related to the specific ventilatory management in our reported population, but such discrepancy further highlights the need of a comprehensive appraisal of pulmonary and chest wall mechanics in COVID-19 patients [20].

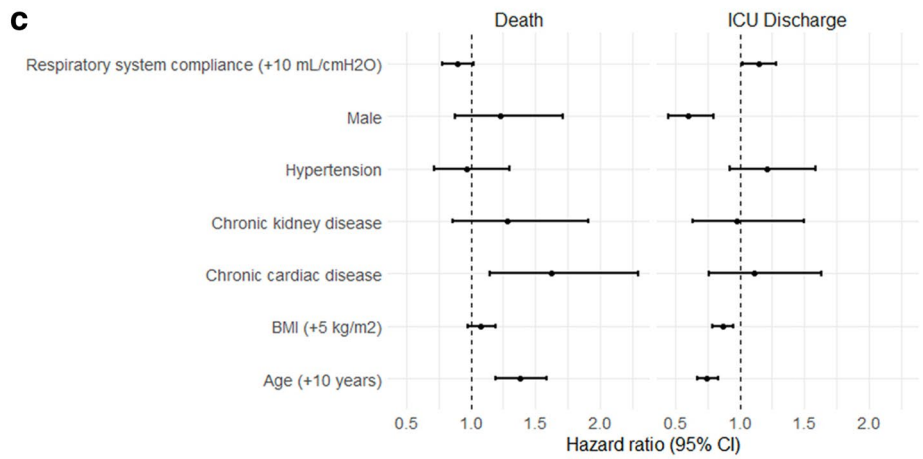
One of the most striking results was the continued use of high PEEP over the first seven days of MV, even in patients with high compliance. This seems counter-intuitive, given that current recommendations in ARDS suggest decreasing PEEP, especially in the face of high compliance. As hypoxemia persisted even with high PEEP and high compliance, our results add to the hypothesis that maintaining high PEEP may worsen gas exchange from lung overdistension, resulting in increased dead space and intrapulmonary shunting. Other authors have speculated that using high levels of PEEP in COVID-19 patients with low recruitability may be detrimental, and that lowering PEEP may improve gas exchange and limit ventilator-induced lung injury [33]. Our results in this large cohort of patients from multiple global areas support this theory. Finally, we found that patients required two weeks of MV, and 28-day mortality in the overall population was 35.6%, with hospital mortality up to 40%. These figures are in line with mortality rates reported by Grasselli [7] in the subgroups characterized by low D-dimer, and mortality in severe-moderate COVID-19 ARDS, as corroborated by Ferrando [6]. Nevertheless, we found that C_{RS} was only associated with the discharge from ICU within 28 days. Thus, the marginal clinical

(See figure on next page.)

Fig. 9 Multistate modelling and Cox regression analysis outcomes for patient with static compliance recorded within 48 h of commencing mechanical ventilation. **a** Multistate model structure for estimating expected outcomes up to 28 days from admission to intensive care unit (ICU). Modelled health states include not on invasive mechanical ventilation (non-MV), on mechanical ventilation (MV), ICU discharge and death. Patients start in the non-MV state if not mechanically ventilated upon or prior to ICU admission, or in the MV state otherwise. **b** Predicted probabilities of occupying health states up to 28 days from ICU admission. **c** Results of Cox proportional hazards modelling for risk of death and ICU discharge from commencement of mechanical ventilation. Covariates comprise age, body mass index (BMI), selected comorbidities (hypertension, chronic cardiac disease, chronic kidney disease) and baseline static compliance. Parameter estimates are presented as estimated hazard ratios with 95% confidence intervals (CI). Further details on factors significantly associated with assessed outcomes are available in the results section


a
Non-MV
MV
ICU Discharge
Death


b
Predicted Probabilities
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Non-MV
ICU Discharge
MV
Death
0
4
8
12
16
20
24
28
Days since ICU admission


c
Death
ICU Discharge
Respiratory system compliance (+10 mL/cmH2O)
Male
Hypertension
Chronic kidney disease
Chronic cardiac disease
BMI (+5 kg/m2)
Age (+10 years)
0.5
1.0
1.5
2.0
0.5
1.0
1.5
2.0
Hazard ratio (95% CI)

value of C_{RS} as a predictor of mortality in COVID-19 patients calls for urgent identification of valuable markers that could inclusively describe pulmonary derangement and guide personalized treatment.

Strengths and limitations

Collaborations between international data collection efforts have the ability to answer many questions related to COVID 19 and to pave the way for future novel diseases to achieve rapid and global data access to help guide best practice. The international COVID-19 Critical Care Consortium study [15], in collaboration with the ISARIC/SPRINT-SARI networks [34], provides inferences not limited by ventilatory management specific to small patient cohort or single-country studies. In addition, in comparison with previous studies, we provided more granular data to inclusively appraise the dynamics of C_{RS} in COVID-19 patients on MV and to study its association with laboratory, and clinical features. A few limitations of our observational study should also be emphasized. First, we centred our analysis on COVID-19 patients, without comparisons against previous repositories of patients with ARDS from different aetiologies. Yet, we provided a wide-ranging discussion of the characteristics of our population in the context of previous analyses in ARDS patients. Second, inferences on pulmonary perfusion disorders in our population can only be speculative, since D-dimer was only available in a small subset of patients (Table 1). Third, as reported by the enrolment rate (Fig. 1 Supplemental Digital Content), patients were mostly enrolled in the early phase of the pandemic, hence extrapolations from our findings should take into account potential biases related to overwhelmed critical care services. Fourthly, it is important to emphasise that we centred our analysis on C_{RS}, but due to the complex respiratory pathophysiology in COVID-19 patients and the high percentage of patients with increased BMI, the use of oesophageal pressure monitoring to fully describe lung and chest wall compliances is advisable and should be prioritised in future investigations. Fifth, the majority of patients were admitted in centers located in North America, Europe and South America. Although these findings are in line with the global distribution of COVID-19 cases, extrapolations of our findings in other regions should be applied cautiously.

Conclusions

Our comprehensive appraisal of COVID-19 patients on MV from a large international observational study implies that expected C_{RS} within 48 h from commencement of MV is not influenced by the duration from onset of symptoms to commencement of MV, but after intubation, a further decrease in C_{RS} might be expected during the first week of ventilation. In addition, baseline C_{RS} is associated with the chance of being discharged from the ICU within 28 days, but it is not a predictive marker of 28-day mortality. Based on potential inferences from our findings, future studies that could provide an in-depth characterization of lungs and chest wall compliance in COVID-19 patients will be critical to guide best practice in ventilatory management.

Abbreviations

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease-2019; COVID-19–CCC/ECMOCARD: COVID-19 Critical Care Consortium incorporating the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease; FiO_2: Inspiratory fraction of oxygen; ICU: Intensive care unit; IQR: Interquartile range; MV: Mechanical ventilation; PBW: Predicted body weight; PEEP: Positive end expiratory pressure; C_{RS}: Static respiratory system compliance.

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GLB conceived the study, participated in its design and coordination and helped to draft the manuscript; JYS conceived the study, participated in its design and coordination and helped to draft the manuscript drafted the manuscript; HD participated in the design of the study and helped to draft the manuscript; NW performed the statistical analysis and helped to draft the manuscript; SS participated in the coordination of the study, performed the statistical analysis and helped to draft the manuscript; JPF participated in the design of the study and helped to draft the manuscript; BL performed the statistical analysis and helped to draft the manuscript; SH participated in the coordination of the study performed the statistical analysis and helped to draft the manuscript; AV performed the statistical analysis and helped to draft the manuscript; GB performed the statistical analysis and helped to draft the manuscript; JEM participated in the design of the study and helped to draft the manuscript; SF participated in the design and coordination of the study and helped to draft the manuscript; MP participated in the coordination of the study helped to draft the manuscript; JL participated in the coordination of the study helped to draft the manuscript; DB participated in the coordination of the study helped to draft the manuscript; EF participated in the coordination of the study helped to draft the manuscript; AT participated in the coordination of the study helped to draft the manuscript; DC participated in the coordination of the study helped to draft the manuscript; AC participated in the design of the study and helped to draft the manuscript; AE participated in collection of data and helped to draft the manuscript; CH participated in coordination and collection of data and helped to draft the manuscript; SI participated in collection of data and helped to draft the manuscript; CL participated in coordination and collection of data and helped to draft the manuscript; SM participated in coordination and collection of data and helped to draft the manuscript; AN participated in coordination and collection of data and helped to draft the manuscript; PY participated in coordination and collection of data and helped to draft the manuscript; MO participated in coordination and collection of data and helped to draft the manuscript; AP participated in coordination and collection of data and helped to draft the manuscript; HTT participated in collection of data and helped to draft the manuscript; JFF conceived the study, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Participating hospitals obtained local ethics committee approval, and a waiver of informed consent was granted in all cases.

Consent for publication
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Statistical analysis
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