An Appraisal of Respiratory System Compliance In Mechanically Ventilated Covid-19 Patients

Gianluigi Li Bassi (✉ g.libassi@uq.edu.au)
University of Queensland  https://orcid.org/0000-0002-0816-0880

Jacky Suen
Critical Care Research Group

Heidi Dalton
Inova Fairfax Hospital

Nicole White
Queensland University of Technology QUT

Sally Shrapnel
University of Queensland - Saint Lucia Campus: The University of Queensland

Jonathon P. Fanning
University of Queensland - Saint Lucia Campus: The University of Queensland

Benoit Liquet
University of Queensland - Saint Lucia Campus: The University of Queensland

Samuel Hinton
University of Queensland - Saint Lucia Campus: The University of Queensland

Aapeli Vuorinem
University of Queensland - Saint Lucia Campus: The University of Queensland

Gareth Booth
University of Queensland - Saint Lucia Campus: The University of Queensland

Jonathan Millar
Roslin University

Simon Forsyth
University of Queensland - Saint Lucia Campus: The University of Queensland

Mauro Panigada
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

John Laffey
National University of Ireland Galway

Daniel Brodie
Columbia University

Eddy Fan
University of Toronto

Antoni Torres
Research

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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 the impact of $C_{RS}$ on the ventilatory management and outcomes of COVID-19 patients on mechanical ventilation (MV), admitted to intensive care units (ICU) worldwide.

Results

We enrolled 318 COVID-19 patients enrolled into the study from January 14th through September 31th, 2020 in 19 countries and stratified into two $C_{RS}$ groups. $C_{RS}$ was calculated as: tidal volume/[(airway plateau pressure-positive end-expiratory pressure (PEEP))] and available within 48 h from commencement of MV in 318 patients. Patients were mean ± SD of 58.0 ± 12.2, predominantly from Europe (54%) and males (68%). Median $C_{RS}$ (IQR) was 34.1 mL/cmH$_2$O (26.5–45.5) and PaO$_2$/FiO$_2$ was 119 mmHg (87.1–164) and was not correlated with $C_{RS}$. Female sex presented lower $C_{RS}$ than in males (95% CI: -13.8 to -8.5 P < 0.001) and higher body mass index (34.7 ± 10.9 vs 29.1 ± 6.0, p < 0.001). Median (IQR) PEEP was 12 cmH$_2$O (10–15), throughout the range of $C_{RS}$, while median (IQR) driving pressure was 12.3 (10–15) cmH$_2$O and significantly decreased as $C_{RS}$ improved (p < 0.001). No differences were found in comorbidities and clinical management between $C_{RS}$ strata. In addition, 28-day ICU mortality and hospital mortality did not differ between $C_{RS}$ groups.

Conclusions

This multicentre report provides a comprehensive account of $C_{RS}$ in COVID-19 patients on MV – predominantly males or overweight females, in their late 50 s – admitted to ICU during the first international outbreaks. Phenotypes associated with different $C_{RS}$ upon commencement of MV could not be identified. Trial documentation: Available at https://www.covid-critical.com/study.

Trial registration
Background

More than 30 million people have been infected by SARS-CoV-2 worldwide, during the first nine months of 2020. Millions have been hospitalized for respiratory complications associated with coronavirus disease-2019 (COVID-19), and close to 20% of those 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, recently, Grasselli and collaborators [7] have compared findings from an Italian repository of COVID-19 ARDS vs. 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. In addition, the authors 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 mono-center 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 14th through September 30, 2020 with a clinically suspected or laboratory confirmed diagnosis of SARS-CoV-2 infection, through real-time PCR. 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$_2$O))]. 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 sec. We computed $C_{RS}$ using the first measured tidal volume, airway plateau pressure and PEEP values, within 48 h of MV commencement. We stratified patients upon the computed median value of our population and compared characteristics of those populations to appraise $C_{RS}$ clinical significance. In the sub-population of patients on controlled MV, without ECMO support, we analysed key pulmonary variables (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**

In the cohort of patients on controlled MV, we made comparisons, adjusted for body mass index, between patients stratified into high and low static $C_{RS}$. The chosen cut-off was based on the resulting distribution of $C_{RS}$ and previous publications [9, 10]. Descriptive statistics are reported using means ± standard deviation or (confidence intervals), or medians (interquartile range) for continuous variables, and numbers (proportions) for categorical variables. We computed estimated p-values for inferential testing to assess changes over time during the period on MV. Bar graphs were used to reveal the changes in key variables over the first seven days of MV. Scatter plots were used to show the association between key respiratory parameters and time. We used a linear mixed model to estimate the strength of association between key respiratory parameters and compliance over time, with a random intercept per patient to adjust for repeated data. ICU outcomes were studied using a multistate model, applied to high and low static CRS separately [19]. Models 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 transitions were modelled by Cox proportional hazards, with outcome right-censored at 28 days from ICU admission. Analyses were conducted using Python version 3.7.7 (The Python Software Foundation) or R version 3.6.2 or higher (The R Foundation).

**Results**

We studied 1452 patients who required MV from January 14 to September 30, 2020. Enrolment rate, since January 2020 is reported in Fig. 1. $C_{RS}$, within 48 h from endotracheal intubation, was available in 318 patients from 19 countries, as reported in Fig. 2. Median $C_{RS}$ (IQR), within the first 48 hours of mechanical ventilation, was 34.1 mL/cmH$_2$O (26.5–45.5) and PaO$_2$/FiO$_2$ 119 mmHg (87.1–164), without any linear association between these parameters. In particular, 17%, 49% and 30% of the patients presented with mild, moderate or severe hypoxemia, respectively (Fig. 3A). Female sex was associated with a significantly lower $C_{RS}$ than in males (95% CI: -13.8 to -8.5 ml/cmH$_2$O P < 0.001), possibly due to higher body mass index (BMI) among females (34.7 ± 10.9 vs 29.1 ± 6.0, p < 0.001) (Fig. 3B). Interestingly, median PEEP was 12 cmH$_2$O (10–15), throughout the range of $C_{RS}$, and median tidal volume was 6.8 mL/Kg of PBW (6-7.5) and delivered at levels greater than 7 ml/Kg of PBW in a proportion of patients with higher $C_{RS}$ (Fig. 4). Furthermore, the resulting median (IQR) static driving pressure was 12.3 (10–15) cmH$_2$O and significantly decreased as $C_{RS}$ improved (p < 0.001). In addition, across the range of $C_{RS}$ PaO$_2$/FiO$_2$ remained consistently below 200 mmHg, while PaCO$_2$ was higher than 45 mmHg. Median (IQR) airway plateau pressure was 26 cmH$_2$O (22–28) and, as expected, a significant association was found between plateau and $C_{RS}$ changes (p < 0.001) (Fig. 5).
Based on the aforementioned median value of $C_{RS}$, patients were stratified into an initial low $C_{RS}$ ($< 34.1 \text{ mL/cmH}_2\text{O}$) group, and high $C_{RS}$ ($\geq 34.1 \text{ mL/cmH}_2\text{O}$). Mean (CI) BMI was higher in patients with low $C_{RS}$ (32.6 kg/m$^2$ (31.0-34.2) vs. 29.3 kg/m$^2$ (28.3–30.2) in patients with high $C_{RS}$, p < 0.001) (Fig. 6). This effect was more pronounced in females, as reported above (Fig. 3). Those classified as having high $C_{RS}$ upon commencement of MV exhibited a drop in $C_{RS}$ over the subsequent seven days, while those in the lower $C_{RS}$ group remained stable throughout (Fig. 7). However, when we considered the evolution of the key pulmonary variables according to the initial $C_{RS}$ (Fig. 8), driving pressure was the only parameter that differed between $C_{RS}$ clusters. Higher $C_{RS}$ was not associated with improved respiratory gas exchange, as detailed by similar levels of hypoxemia and hypercapnia between the $C_{RS}$ groups. PEEP fell over days but remained greater than 12 cmH$_2$O across $C_{RS}$ strata (Fig. 8), even in those with high $C_{RS}$. In addition, PEEP did not change according to the level of oxygen saturation (Fig. 9), but its increase was in line with the increase of FiO$_2$ and independent of the set tidal volume. Finally, higher PEEP was closely associated with worse oxygenation levels and hypercapnia (Fig. 10).

Baseline characteristics upon ICU admission, applied interventions and outcomes, stratified by $C_{RS}$, are summarized in Table 1. No differences were found in comorbidities and clinical management between $C_{RS}$ strata. The duration of MV was on average two weeks and similar between patients with different initial $C_{RS}$. Finally, competing risks analysis of ICU outcomes for the two groups is shown in Fig. 11. Overall 28-day mortality for low and high $C_{RS}$ after accounting for competing risk was 20.6% (95%CI = 13.7–27.5%) and 31% (95% CI = 21.4–40.6%), respectively. From commencement of MV, estimated 28-day mortality was 24.5% (95%CI 17.4–31.6%) in low $C_{RS}$ and 23.1% (95%CI = 16.6–29.6%) in high $C_{RS}$.
**Table 1**
Characterization and management of COVID-19 patients stratified by respiratory system compliance

| Parameter                                                                 | All (N = 318)* | $C_{RS} < 34.1 \text{ mL/cmH}_2\text{O}$ (N = 159) | $C_{RS} \geq 34.1 \text{ mL/cmH}_2\text{O}$ (N = 159) | P-value |
|--------------------------------------------------------------------------|----------------|-----------------------------------------------|-----------------------------------------------|---------|
| Age N. Mean (SD) y                                                      | 318            | 159                                           | 159                                           | 0.51    |
|                                                                            | 58 (12.2)      | 58 (12.4)                                     | 59 (11.9)                                     |         |
| Female N. (%)                                                            | 102 (32)       | 78 (49)                                       | 24 (15)                                       | < 0.001 |
| Geographic region N. (%)                                                 |                |                                               |                                               | < 0.001 |
| Africa                                                                   | 25 (8)         | 20 (13)                                       | 5 (3)                                         |         |
| Asia                                                                     | 21 (7)         | 16 (10)                                       | 5 (3)                                         |         |
| Australia and New Zealand                                                | 4 (1)          | 1 (1)                                         | 3 (2)                                         |         |
| Europe                                                                   | 172 (54)       | 60 (38)                                       | 112 (70)                                      |         |
| Latin America and the Caribbean                                          | 12 (4)         | 7 (4)                                         | 5 (3)                                         |         |
| Northern America                                                         | 84 (26)        | 55 (35)                                       | 29 (18)                                       |         |
| Time from onset of symptoms to hospital admission. N.                   | 314            | 158                                           | 156                                           | 0.042   |
| Median (IQR) days                                                        | 8 (4–10)       | 8 (4–10)                                      | 8 (6–12)                                      |         |
| Time from onset of symptoms to ICU admission Median (IQR days)           | 314            | 158                                           | 156                                           | 0.31    |
|                                                                            | 8 (6–12)       | 8 (5–12)                                      | 8 (6–12)                                      |         |
| Time from Onset symptoms to mechanical ventilation Median (IQR) days     | 314            | 158                                           | 156                                           | 0.34    |
|                                                                            | 8 (6–12)       | 8 (6–12)                                      | 8 (7–12)                                      |         |
| **CLINICAL SIGNS AND LABORATORY FINDINGS UPON ICU ADMISSION**            |                |                                               |                                               |         |
| WBC count N. Median (IQR) 10*3/µL                                         | 228            | 111                                           | 117                                           | 0.60    |
|                                                                            | 8.3 (6.2–12.3) | 8.2 (6.2–11.9)                               | 8.8 (5.9–13.3)                               |         |
| Lymphocyte count N. Median (IQR) 10*3/µL                                  | 166            | 79                                            | 87                                            | 0.82    |
|                                                                            | 0.8 (0.5–1.3)  | 0.8 (0.5–1.3)                                | 0.8 (0.5–1.2)                                |         |
| Parameter                                      | All \( N = 318^* \) | \( C_{RS} < 34.1 \text{ mL/cmH}_2\text{O} \) \( N = 159 \) | \( C_{RS} \geq 34.1 \text{ mL/cmH}_2\text{O} \) \( N = 159 \) | P-value |
|------------------------------------------------|----------------------|----------------------------------------------------------|----------------------------------------------------------|---------|
| Temperature N. Median (IQR) °C                  | 204 (37.4 (36.5–38.1)) | 103 (37.2 (36.5–38.0)) | 101 (37.6 (36.7–38.3)) | 0.15    |
| Creatinine N. Median (IQR) mg/dL                | 233 (0.9 (0.7–1.4)) | 113 (1.0 (0.7–1.6)) | 120 (0.9 (0.7–1.2)) | 0.11    |
| CRP N. Median (IQR) mg/dL                       | 148 (96 (15–163)) | 59 (100 (17–195)) | 89 (83 (15–146)) | 0.28    |
| Lymphocyte count to CRP ratio N. Median (IQR)   | 106 (0.01 (0.00–0.08)) | 44 (0.01 (0.00–0.03)) | 62 (0.02 (0.00–0.08)) | 0.18    |
| Neutrophil to lymphocyte ratio N. Median (IQR)  | 143 (9 (5–14)) | 71 (8 (4–14)) | 72 (10 (6–15)) | 0.27    |
| D-dimer level mg/L N. Median (IQR)              | 31 (1.3 (0.8–3.5)) | 19 (1.3 (0.9–5.1)) | 12 (1.3 (0.7–2.6)) | 0.73    |

**CLINICAL MANAGEMENT DURING ICU ADMISSION**

| Parameter                                      | All (%) | \( C_{RS} < 34.1 \text{ mL/cmH}_2\text{O} \) (%) | \( C_{RS} \geq 34.1 \text{ mL/cmH}_2\text{O} \) (%) | P-value |
|------------------------------------------------|---------|--------------------------------------------------|--------------------------------------------------|---------|
| Antibiotics                                    | 311 (98) | 158 (99) | 153 (96) | 0.12    |
| Antivirals                                     | 202 (64) | 92 (58)  | 110 (69) |         |
| Continuous renal replacement therapy N. (%)    | 27 (8)   | 17 (11)  | 10 (6)   | 0.14    |
| Vasoactive drugs N. (%)                        | 62 (19)  | 35 (22)  | 27 (17)  | 0.32    |
| Cardiac-assist devices N. (%)                  | 29 (9)   | 13 (8)   | 16 (10)  | 0.70    |
| ECMO N. (%)                                    | 33 (10)  | 18 (11)  | 15 (9)   | 0.72    |
| Prone Positioning N. (%)                       | 178 (56) | 90 (57)  | 88 (55)  | 0.91    |
| iNO N. (%)                                     | 33 (10)  | 19 (12)  | 14 (9)   | 0.47    |
| Neuromuscular blockade N. (%)^                 | 261 (82) | 134 (84) | 127 (80) | 0.38    |
| Parameter                                      | All (N = 318)* | CRs < 34.1 mL/cmH₂O (N = 159) | CRs ≥ 34.1 mL/cmH₂O (N = 159) | P-value |
|-----------------------------------------------|----------------|-------------------------------|-------------------------------|---------|
| Recruitment maneuvers N. (%)                  | 146 (46)       | 76 (48)                       | 70 (44)                       | 0.58    |
| Duration of mechanical ventilation N.         |                |                               |                               |         |
| Median (IQR) days                            | 270            | 126                           | 144                           | 0.94    |
|                                               | 14 (8–24)      | 14 (8–25)                     | 13 (8–24)                     |         |
| Duration of ICU stay N.                       |                |                               |                               | 0.80    |
| Median (IQR) days                            | 275            | 132                           | 143                           |         |
|                                               | 18 (10–30)     | 18 (9–30)                     | 18 (10–30)                    |         |
| Duration of Hospital stay                     |                |                               |                               | 0.83    |
| N. Median (IQR) days                         | 270            | 130                           | 140                           |         |
|                                               | 28 (16–44)     | 27 (16–44)                    | 28 (15–44)                    |         |
| OUTCOMES N (%)                                |                |                               |                               |         |
| Discharged from ICU to Hospital Wards        | 44 (14)        | 17 (11)                       | 27 (17)                       | NS      |
| Discharged from Hospital                      | 112 (35)       | 59 (37)                       | 53 (33)                       | NS      |
| Transfer to another hospital                  | 41 (13)        | 18 (11)                       | 23 (14)                       | NS      |
| Palliative discharge                          | 1 (0)          | 1 (1)                         | 0 (0)                         | NS      |
| Death or hospital discharge status still      | 29 (9)         | 20 (13)                       | 9 (6)                         | NS      |
| unknown                                       |                |                               |                               |         |
| 28-Day ICU Mortality                          | 76 (24)        | 37 (23)                       | 39 (25)                       | > 0.99  |
| Hospital Mortality                            | 91 (29)        | 44 (28)                       | 47 (30)                       | 0.11    |

Table 1 caption

*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 48h from commencement of mechanical ventilation. Percentages are calculated for non-missing data. ^Administration of neuromuscular blockade drugs administered during the first day of invasive mechanical ventilation was not included in the analysis. IQR, interquartile range; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; NS, not significant.

Discussion
This large observational report from ICU's throughout the world found no association with initial static respiratory system compliance and major outcomes. Interestingly, lower $C_{RS}$ was found in female patients, who also presented higher BMI upon admission. Ventilatory management across $C_{RS}$ strata was remarkably similar and the use of relatively high PEEP levels was maintained throughout the mechanical ventilation period – first 7 days – despite $C_{RS}$ measures.

In comparison with previous reports on ARDS patients without COVID-19 [20], 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 [21, 22], as expected, patients with higher BMI had lower $C_{RS}$, and this was most notable in female patients, who 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, should be further explored. We also found that in both $C_{RS}$ strata, plateau pressure and driving pressure were within what is typically presumed as lung protective ranges [23]. As many of these patients were obese, this raises the question of whether these modest pressures might have increased the risk of pulmonary derecruitment, as shown by a decrease in $C_{RS}$ (Fig. 5 Supplemental Digital Content) and 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 [24], but more research is needed to corroborate such reasoning.

Phenotypic subsets of COVID-19-associated ARDS have been proposed [9, 13, 17, 18, 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$_2$O, 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 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, 18]. As corroborated by landmark post-mortem studies [28] and clinical studies [7, 29], SARS-CoV-2 heterogeneously affect 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, median $C_{RS}$ value found in our population was 34.1 ml/cmH$_2$O, similar to findings by Ferrando et al [6], not dissimilar to findings by
Bellani et al on patients with non-COVID-19 ARDS [30], but lower than figures recently reported by Grasselli [7] and Grieco [31] in COVID-19 patients. This could have been related to the higher BMI 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 [22].

Irrespective of $C_{RS}$, we observed substantial similarities in the management of patients with diverse $C_{RS}$. 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 (Fig. 2 Supplemental Digital Content). This seems counterintuitive, given that current recommendations in ARDS suggest decreasing PEEP, especially in the face of high compliance. As hypoxemia and hypercapnia persisted even with high PEEP and high compliance (Fig. 5 Supplemental Digital Content), 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 [32]. Our results in this large cohort of patients from multiple global areas support this theory. Finally, we found that patients often required two weeks of MV, and we could not find any difference in major outcomes between $C_{RS}$ strata. In particular, 28-day mortality in the overall population was 24%, with hospital mortality up to 29% (Table 1). These figures are in line with mortality rates reported by Grasselli [7] in the subgroups characterized by low D-dimer, and mortality in moderate and mild COVID-19 ARDS as corroborated by Ferrando [6]. Nevertheless, the marginal clinical value of $C_{RS}$ in COVID-19 patients calls for urgent identification of novel valuable markers that could inclusively describe pulmonary derangement and guide personalized treatment to improve outcomes.

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 [33], 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.
Conclusions

Our comprehensive appraisal of COVID-19 patients on MV from a large international observational study implies that initial $C_{RS}$ is not associated with major outcomes, emphasizing limitations in the clinical use of $C_{RS}$ as a predictive marker, specifically in obese patients. Indeed, irrespective of the $C_{RS}$ values, consistent ventilatory and clinical management was provided. Based on potential inferences from our findings, future studies that could provide an in-depth characterization of pulmonary mechanics in COVID-19 will be critical to guide best practice in ventilatory management.

Abbreviations

• Acute respiratory distress syndrome (ARDS)
• Coronavirus disease-2019 (COVID-19)
• COVID-19 Critical Care Consortium incorporating the ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (COVID-19–CCC/ECMOCARD)
• Inspiratory fraction of oxygen (FiO2)
• Intensive care unit (ICU)
• Interquartile range (IQR)
• Mechanical ventilation (MV)
• Predicted body weight (PBW)
• Positive end expiratory pressure (PEEP)
• Static respiratory system compliance (CRS)

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

Not applicable

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

**Competing interests**

GLB and JF received research funds, through their affiliated institution from Fisher & Paykel. All remaining authors do not have any conflict of interest related to this report.

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**Authors’ contribution**

A/Prof Li Bassi and Dr. Suen, who equally contributed to this work, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design*: Gianluigi Li Bassi; Jacky Y. Suen; Heidi J. Dalton; and John F. Fraser *Acquisition, analysis, or interpretation of data*: Gianluigi Li Bassi; Jacky Y. Suen; Heidi J. Dalton; Nicole White; Sally Shrapnel; Jonathon P. Fanning; Benoit Liquet; Samuel Hinton; Aapeli Vuorinem; Gareth Booth; Jonathan E. Millar; Simon Forsyth; Mauro Panigada; John Laffey; Daniel Brodie; Eddy Fan; Robert Bartlett; Antoni Torres; Davide Chiumello; Amanda Corley; Alyaa Elhazmi; Carol Hodgson; Shingo Ichiba; Carlos Luna; Srinivas Murthy; Alistair Nichol; Pauline Yeung; Mark Ogino; Antonio Pesenti; Huynh Trung Trieu; and John F. Fraser

*Drafting of the manuscript*: Gianluigi Li Bassi; Jacky Y. Suen; Heidi J. Dalton; Nicole White; Sally Shrapnel; Jonathon P. Fanning; Benoit Liquet; Samuel Hinton; Aapeli Vuorinem; Gareth Booth; Jonathan E. Millar; Simon Forsyth; Mauro Panigada; John Laffey

*Critical revision of the manuscript for important intellectual content*: Daniel Brodie; Eddy Fan; Robert Bartlett; Antoni Torres; Davide Chiumello; Amanda Corley; Alyaa Elhazmi; Carol Hodgson; Shingo Ichiba; Carlos Luna; Srinivas Murthy; Alistair Nichol; Pauline Yeung; Mark Ogino; Antonio Pesenti; Huynh Trung Trieu; and John F. Fraser

*Statistical analysis*: Nicole White; Sally Shrapnel; Benoit Liquet; Samuel Hinton; Aapeli Vuorinem; Gareth Booth.

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Gabriella Abbate, RN, MSc; Ryuzo Abe, MD; Shingo Adachi, MD; Takako Akimoto, MD; Abdulrahman Al-Fares, MD; Huda Alfaourdi, MD; Abdullah Al-Hudaib, MD; Massimo Antonelli, MD; Christel Arnold-Day, MD; Lovkesh Arora, MD; Michaela Barnikel, MD; Peter Barrett, MD; Aleksandr Beljantsev, MD; Suzanne Bennett, MD; Amar Bhatt, MD; Pablo Blanco-Schweizer, MD; Luca Brazzi, MD; Nicolas Brozzi, MD; Sara Buabbaas, MD; Nina Buchtele, MD; Erlina Burhan, MD; Hergen Buscher, MD; Mara Caroline, MD; Edmund G. Carton, MD; Enrique Chicote Álvarez, MD; Adrian Ceccato, MD; Silvia Coppola, MD; Hwa Jin Cho, MD; Sung-Min Cho, DO, MHS; Young-Jae Cho, MD; Anna Ciullo, MD; Sebastiano Colombo, MD; Sofía Contreras, MD; Alberto Cucino, MD; Al-Awwab Dabaliz, MD; Andrea Dell'Amore, MD; Mehul Desai, MD; Esther Dreier, MD; Lucian Durham, MD; Tarek El-Shazly, MD; Octavio Falcucci, MD; Shu Fang, MPH; Arie Zainul Fatoni, MD; Mohamed Fayed, MD; Riccardo Ferrer Roca, PhD; Kirsten M. Fiest, PhD; Cathleen Fomey, MD; Giuseppe Foti, MD; Shigeki Fujitani, MD; Masahiro Fukuda, MD; Sérgio Gaião, MD; Johannes Gebauer, MD; Marco Giani, MD; Eric Gnall, MD; Jerónimo Graf, MD; R. Wilson Grandin, MD; Giacomo Grasselli, MD; Anna Greti, MD; Matthew Griffee, MD; Halah Hassan, BMS; Ibrahim Hassan, MD; Silver Heinsar, MD; Jaime Hernandez-Montfort, MD; Kanako Horibe, MD; Koji Hoshino, MD; Kenta Hoshino, MD; Ali Ait Hssain, MD; Jeffrey Javidfar, MD; Inseok Jeong, MD; Juan Masa Jiménez, MD; Anne Joosten, MD; Mark Joseph, MD; Jae-Seung Jung, MD, PhD; Ruth Noemí Jorge García, MD; Varun A Karnik, BSc; Daisuke Kasugai, MD; Christy Kay, MD; Katrina Ki, PhD; Irfan Khan, MD; Jae-Bum Kim, MD; Ethan Kurtzman, MBA, RRT-NPS; Su Hwan Lee, MD; Keibun Liu, MD, PhD; Michela Leone, MD; Antonio Loforte, MD; Roberto Lorusso, MD, PhD; Gösta Lotz, MD; India Lye, RN; Olavi Maasikas, MD; Lars Maier, MD; Maximilian Malferttheiner, MD, PhD; Angela Maria Marulanda Yantén, MD; Eva Marwali, MD; Danny McAuley, MD, PhD; Colin McCloskey, MD; Angela McBride, MD; Dan Meyer, MD; Brook Mitchell, MD; Nahush A. Mokadam, MD; Giorgia Montrucchio, MD; Rita Moreno, MD; Naoki Moriyama, MD; Andrea Moscatelli, MD; Ana Motos, MSc; Paolo Navalesi, MD; Wing Yiu Ng, MD; Hollier F. O'Neill, BMS; Nchafatso Obonyo, MD, PhD; Tawnya Ogston, MD; Getter Öigus, MD; Shinichiro Ohshimo, MD; Erik Osborn, MD; Javier Osatnik, MD; Clark Owyang, MD; Ken Kuljit S. Parhar, MD, MSc; Giles Peek, MD; Paolo Pelosi, MD; Leticia Pretti Pimenta, MD; Mohammed Abraar Quraishi, MD; Kollengode Ramanathan, MD; Indrek Rätsep, MD; Janice D. Reid, BSc; Jordi Riera, MD, PhD; Diego Bautista Rincón, MD; Roberto Roncon-Albuquerque, MD; Kristina Rudolph BSN, RN; Angel Sanchez, MD; Gabrielle Sales, MD; S. Veena Satyapriya, MD; Kei Sato, MD; Stephan Schroll, MD; Michael Schwameis, MD; Tamara Seitz, MD; Timothy Shapiro, MD; Kiran Shekar, MD, PhD; Takashi Shimazui, MD; Hiroaki Shimazu, MD; Naoki Shimizu, MD; Hoi-Ping Shum, MD; Malcolm Sim, MBBch, MD; Dominic So, MD; Tae Song, MD; Henry T. Stelfox MD, PhD; Madhu Subramanian, MD; Stephanie-Susanne Stecher, MD; Subbarao Elapavaluru, MD; Konstanty Szuldrzynski, MD; Hiro Tanaka, MD; Hayato Taniguci, MD; Azhari Taufik, MD; Shaun Thompson, MD; David Thomson, MD; Yuka Uchimami, MD; Asad Ali Usman, MD, MPH; Jorge Velasco, MD; Karin S. Wildi MD; Emily Wood; Masaki Yamasaki, MD; Minlan Yang, MD; Stephanie Yerkovich, PhD; Toshiki Yokoyama, MD; Saptadi Yularito, MD; Ana Loza Vazquez, MD; Bhishoy Zakhary, MD; Alberto Zanella, MD; Courtney Dwyer.

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Figures
Figure 1

Patient enrolment rate from January 14th through September 30, 2020. As depicted, the majority of patients were enrolled between March and May 2020.
Figure 2

Patient population flow chart. The analysis of 1452 COVID-19 patients on mechanical ventilation identified 318 patients with respiratory system compliance within 48h from commencement of mechanical ventilation.
Figure 3

A: Linear mixed model analysis of arterial partial pressure of oxygen (PaO2/FiO2) and respiratory system compliance (CRS), based on the first measurement obtained within 48h from commencement of mechanical ventilation, with an interaction of gender and adjusted for body mass index (BMI). No statistically significant association was found between PaO2/FiO2 and CRS. The vertical dashed black line stratifies compliance into low and high compliance, based on the median value of the population.
(34.1 mL/cmH2O). Typical acute respiratory distress syndrome stratification groups [34] (severe, moderate and mild based on levels of hypoxemia) are highlighted in light red, yellow and green, respectively. B: Static respiratory system compliance (CRS) distribution by sex, based on the first measurement obtained within 48h from commencement of mechanical ventilation, and grouped by low (< 34.1 mL/cmH2O, light red) or high (≥ 34.1 mL/cmH2O, light blue). Dashed black lines depict median values for females and males.

Figure 4

Association of key pulmonary variables with respiratory system compliance during the first 7 days of mechanical ventilation. 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, which was found to be associated with PaO2/FiO2 (p=0.017), PaCO2 (p=0.034), PEEP (p<0.001) and driving pressure (p<0.001). No statistically significant difference was found between respiratory system compliance and FiO2 (p = 0.121). Patients with better respiratory system compliance were ventilated with slightly larger tidal volumes (0.039 mL/Kg of PBW for every unit increase (ml/cmH2O) of compliance, p<0.001). PEEP was also associated with respiratory system compliance (0.033 cm/H20 increase in PEEP for every one unit increase (ml/cmH2O) of compliance, p<0.001). Finally, driving pressure decreased on average 0.233 cm/H20 for every unit increase (ml/cmH2O) of compliance (p<0.001.). PaO2/FiO2, ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen; PaCO2 arterial partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure.
Figure 5

Association airway plateau pressure with static respiratory system compliance. Linear Mixed model analysis of the association of respiratory system compliance with airway plateau pressure during the first 7 days of mechanical ventilation (colour 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 (p<0.001), but based on the model prediction, airway plateau pressure remained predominantly below 30 cmH2O even toward the worst range of compliances.
Figure 6

Body mass index by respiratory system compliance stratification. Grey line of the boxplot shows median body mass index (BMI), while the upper and lower lines depict interquartile range. BMI varied between respiratory system compliance groups (p<0.001). CRS, respiratory system compliance.
Figure 7

Respiratory system compliance dynamics. Evolution of respiratory system compliance (CRS) over the first 7 days of mechanical ventilation stratified by initial CRS within 48h from commencement of mechanical ventilation. Under each day, the number of analysed patients is reported in parenthesis. Per each graph, fitted line of the model is depicted and the upper and lower lines display the 95% predictive interval. Respiratory system compliance during the first seven days of mechanical ventilation worsened only in patients who initially presented with higher CRS (p<0.001). CRS, respiratory system compliance.
Figure 8

Evolution of key pulmonary variables over the first 7 days of mechanical ventilation stratified by the static compliance of respiratory system (CRS) within the first 48h of mechanical ventilation. Under each day, the number of analysed patients is reported in parenthesis. Per each graph, fitted line of the model is depicted and the upper and lower lines display the 95% predictive interval. Throughout the days, although as expected, driving pressure was lower in the low CRS group, no other significant differences among compliance levels were found. Yet, PaCO2 and driving pressure increased significantly and steadily in both groups (p<0.01); while PEEP and FiO2 decreased significantly (p<0.001). PaO2/FiO2, ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen; PaCO2 arterial partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure.
Figure 9

Applied PEEP levels based on levels of oxygen saturation and association with key ventilatory settings. Linear Mixed model analysis of pulmonary variables and mechanical ventilator settings vs. PEEP during the first 7 days of mechanical ventilation (colour 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. PEEP increased accordingly with the increase in inspiratory fraction of oxygen (p<0.001.). Conversely, PEEP was not significantly associated with oxygen saturation (p=0.821) or tidal volume (p=0.106.). PEEP, positive end expiratory pressure.

Figure 10
Association between PEEP levels and gas exchange. Evolution of PEEP over the first 7 days of mechanical ventilation stratified by initial CRS within 48h from commencement of mechanical
ventilation. Per each graph, fitted line of the model is depicted and the upper and lower lines display the 95% predictive interval. A: PEEP level was inversely associated with PaO2/FiO2 (p<0.001), comparably between CRS groups. Likewise, B: PEEP level was associated with PaCO2 (p<0.01), in a similar fashion between CRS groups. PEEP, positive end-expiratory pressure; PaO2/FiO2, ratio between arterial partial pressure of oxygen and inspiratory fraction of oxygen; PaCO2 arterial partial pressure of carbon dioxide.

Figure 11
Outcomes from multistate model analysis up to 28 days from intensive care unit admission. Subfigures are stacked probability plots for the model states Non-MV (not mechanically ventilated), MV (on mechanical ventilation), Discharge from ICU and Death. Upper section (LOW CRS) depicts patients with low static respiratory compliance (CRS < 34.1 mL/cmH2O). Overall 28-day mortality for low CRS after accounting for competing risk was 20.6% (standard error (SE) = 3.5%; 95% CI = 13.7% - 27.5%). From commencement of mechanical ventilation, estimated 28-day mortality was 24.5% (SE = 3.6%; 95% CI = 17.4% - 31.6%). Lower section (HIGH CRS) shows patients with high respiratory compliance (CRS ≥ 34.1 mL/cmH2O). Overall 28-day mortality for high CRS after accounting for competing risk was 31% (SE = 4.9%; 95% CI = 21.4% - 40.6%). From commencement of mechanical ventilation, estimated 28-day mortality for this group was 23.1% (SE = 3.3%; 95% CI = 16.6% - 29.6%).